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Risk factors related to acute respiratory distress syndrome and death in patients with COVID-19: a retrospective cohort study in Wuhan, China

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Abstract

Background:

The COVID-19 pandemic has been considered a great threat to global public health. We aimed to clarify the risk factors associated with the development of acute respiratory distress syndrome (ARDS) and progression from ARDS to death and construct a risk prediction model.

Methods:

In this single-centered, retrospective, and observational study, 796 COVID-19 patients developed ARDS and 735 COVID-19 patients without ARDS were matched by propensity score at an approximate ratio of 1:1 based on age, sex and comorbidities. Demographic data, symptoms, radiological findings, laboratory examinations, and clinical outcomes were compared between those with or without ARDS. Univariable and multivariable logistic regression models were applied to explore the risk factors for development of ARDS and progression from ARDS to death and establish a comprehensive risk model.

Results:

Higher SOFA, qSOFA, APACHE II and SIRS scores, elevated inflammatory cytokines, dysregulated multi-organ damage biomarkers, decreased immune cell subsets were associated with higher proportion of death (34.17% vs 1.22%; *P*<0.001) and increased risk odds of death (OR=57.216, 95%CI=28.373-115.378; *P*<0.001) in COVID-19 patients with ARDS. In addition to previous reported risk factors related to ARDS development and death, such as neutrophils, IL-6, D-Dimer, leukocytes and platelet, we identified elevated TNF-α (OR=1.146, 95%CI=1.100-1.194; *P*<0.001), CK-MB (OR=1.350, 95%CI=1.180-1.545; *P*<0.001), declined ALB (OR=0.834, 95%CI=0.799-0.872; *P*<0.001), $CD8^+$ T cells (OR=0.983, 95%CI=0.976-0.990; *P*<0.001) and $CD3^-CD19^+$ B cells (OR=0.992, 95%CI=0.988-0.997; *P*=0.003) as novel risk factors. Most importantly, the predictive accuracy of the combined model integrating four score systems and these risk factors demonstrated highest among all models for the development of ARDS (AUC= 0.904) and the progression from ARDS to death (AUC= 0.959).

Conclusion:

COVID-19 patients with ARDS were more likely to develop into death. The potential risk factors and the comprehensive prediction model could be helpful to identify patients that are at risk of developing ARDS with poor prognosis at an early stage, which might help physicians to formulate a timely therapeutic strategy.

Background

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) has become a global pandemic. As of June 18, 2020, a total of 8,242,989 COVID-19 cases were confirmed globally with 445,535 deaths.[1] Moreover, It is now clear that among hospitalized patients

with COVID-19, pneumonia, sepsis, and respiratory failure are frequent complications, with some patients predisposed to poor clinical outcomes[2,3], while uncertainty regarding management of the complications arose in the course of this viral illness.[4] To reasonably improve the prognosis of COVID-19 patients with complications, effective risk stratification and early intervention for patients are urgently needed.

The pathological study of biopsy specimens from COVID-19 patients has shown that the lung are the target organ for COVID-19 and the patients who develop acute lung injury are susceptible to acute respiratory distress syndrome (ARDS).[5] Furthermore, ARDS is one of the most common critical complications and eventually might develop into severe systemic disease and multiple organ failure threatening the life safety of patients during deterioration of COVID-19.[6] The sequential organ failure assessment (SOFA), quick SOFA (qSOFA), acute physiology and chronic health evaluation II (APACHE II) and systemic inflammatory response syndrome (SIRS) scores have been considered as good evaluation indexes for sepsis, septic shock, multi-organ dysfunction and even death in patients suffering from bacterial or viral pathogen infection.[7-12] Notably, accumulative evidence has shown that SARS-CoV-2 caused inflammatory infiltration of interstitial mononuclear cells is related to disease progression from ARDS to death.[5] Additionally, initial analyses of the patients with ARDS had shown that older age, high fever, neutrophilia, organ and coagulation dysfunction, and elevated D-Dimer levels were the risk factors associated with development of ARDS and death.[13,14] However, due to the limitation of small sample size in previous studies, large studies are needed to fully describe the detailed biochemical biomarkers and risk factors related to adverse clinical outcomes of COVID-19 patients who develop ARDS. Most importantly, it is urgent to develop a comprehensive prediction model integrating these scores and risk factors associated with the development and progression of ARDS in patients with COVID-19, which is potential of great value for risk assessment, identification of disease-related biomarkers and provision of appropriate treatment.

In this single-centered, retrospective study, we performed a comprehensive analysis of the clinical features of patients with COVID-19 and ARDS admitted to Tongji Hospital, Wuhan. We provide a full clinical description of ARDS and non-ARDS patients, as well as survivors and non-survivors, and explore risk factors for ARDS and death in hospital patients. Finally, we aimed to construct a comprehensive risk prediction model by combining risk factors and scores, which is beneficial for identification of development of ARDS and determination of effective treatments in COVID-19 patients within 24 hours after admission.

Methods

Study Design and Participants

This is a single-center, retrospective cohort study of COVID-19 patients with confirmed SARS-COV-2 infection from Tongji Hospital, a designated hospital for severely or critically ill patients in Wuhan, China. A total of 3256 COVID-19 patients were diagnosed by WHO Interim guidance[15] and admitted from January 13, 2020, to March 31, 2020. Among these patients, 796 COVID-19 patients with ARDS were

enrolled and 735 COVID-19 patients without ARDS were statistically matched by propensity score based on age, sex and comorbidities with an approximate ratio of 1: 1. The comorbidities included hypertension, diabetes, coronary heart disease, hepatitis, chronic obstructive pulmonary disease, chronic bronchitis and pulmonary tuberculosis. This study was approved by the Ethics Committee of Tongji Hospital Tongji Medical College, HUST, and waived informed consent of all participants.

Data Collection

The clinical retrospective data was retrieved through the electronic medical records of Tongji Hospital, including demographic characteristics, medical history, initial symptoms, laboratory findings, CT findings and treatment. The admission and hospitalized data of these patients were collected, reviewed and verified by a trained team of physicians. If the data was missing, uncertain or needed to be clarified, it would be collated and verified through communication with involved health-care providers or patients and their families.

Definitions

The ARDS patients were diagnosed based on the Berlin Definition.[16] Throat swab samples were obtained to identify SARS-CoV-2 infection at admission and tested by real-time RT-PCR methods. The scores of SOFA, qSOFA, APACHE II and SIRS were calculated according to the physiological and laboratory parameters within 24 hours after admission. Details of these four scores and were presented in supplementary methods [see Additional file 1].

Statistical analysis

Continuous variables are expressed as median and interquartile range (IQR) or mean and standard deviation (SD), and categorical variables are expressed as numbers and percentages (%). For continuous variables, Student's t-test was applied to normal distribution data, and Mann-Whitney U non-parameter test was applied to non-normal distribution data. Pearson's χ^2 test or Fisher's exact test was performed for categorical variables. Logistic regression models were used to estimate odds ratio (ORs) and 95% confidence intervals (95%CIs) to evaluate risk factors on the development and death risk of COVID-19 patients. The multivariate logistic model analysis was used to establish death risk prediction models. The significant variables from univariable analysis were considered as the candidates. Receiver operating characteristic (ROC) curves and area under the curve (AUC) was used to assess the predictive accuracy of each model. A two-sided P value<0.05 was considered statistically significant. All statistical analyses were performed with SPSS (23.0), or R software (3.6.0).

Detailed methods can be seen in supplementary methods [see Additional file 1]

Results

Clinical characteristics and laboratory findings

796 (51.99%) COVID-19 patients with ARDS and 735 (48.01%) COVID-19 patients without ARDS were statistically matched by age, sex, and comorbidities in this study. The COVID-19 patients with ARDS were further classified into survivors (65.83%) and non-survivors (34.17%). Expectedly, COVID-19 patients with ARDS were more prevalent to be admitted to the intensive care unit (ICU) (19.24% vs 0.42%; *P*<0.001) and had a higher proportion of death (34.17% vs 1.22%; *P*<0.001) than those without ARDS (Table 1).

As shown in Table 1, symptoms such as fever (84.73% vs 61.23%; *P*<0.001), dyspnea (43.51% vs 35.63%; *P*=0.003) , fatigue(18.78% vs 14.22%; *P*=0.022), and vertigo (5.00% vs 2.25%; *P*=0.006) were more prevalent in COVID-19 patients with ARDS. Fever (89.52% vs 82.32%; *P*=0.010), dyspnea (50.00% vs 40.20%; *P*=0.012) and vertigo (7.30% vs 3.90%; *P*=0.045) were more pronounced in non-survivors (Table2). Moreover, patchy shadows and bilateral pulmonary involvement were found in majority of COVID-19 patients, while the difference of patchy shadows was not statistically significant between patients with and without ARDS (Table 1).

We observed that the levels of inflammatory cytokines were substantially elevated in patients with ARDS, including IL-6 (13.24 vs 3.11 pg/mL; *P*<0.001),hs-CRP (47.80 vs 5.20 pg/mL; *P*<0.001), TNF-α (8.30 vs 7.30 pg/mL; *P*<0.001). Conversely, the counts of immune cell subsets, including $CD3^+CD19^-$ T cells (845.00 vs 1073.00 /μL; *P*<0.001), $CD8^+$ T cells (279.00 vs 344.00 /μL; *P* <0.001), $CD3^-CD16^+CD56^+$ NK cells (138.00 vs 192.00/μL; *P*<0.001) as well as the total number of T cells, B cells and NK cells (1194.00 vs 1545.00 /μL; *P*<0.001), were significantly decreased in the patients with ARDS (Table 1).

We also observed dysregulated cardiac injury biomarkers, liver damage indexes and coagulation biomarkers were more pronounced in patients with ARDS. Our study showed that significantly increased CK-MB (0.80 vs 0.70 U/L; *P*<0.001), creatinine (72.50 vs 70.00 μmol/L; *P*=0.009), D-Dimer (1.12 vs 0.43 ug/mL; *P*<0.001) and FDP (5.20 vs 4.00 g/L; *P*<0.001), while decreased ALB (34.30 vs 38.60 g/L; *P<0.001*) presented in ARDS group (Table 1). Compared with survivors, the same results can be found in non-survivors (Table 2). Other laboratory indexes in patients with and without ARDS, as well as non-survivors and survivors, were presented in Supplementary Table 1 [see Additional file 2] and Supplementary Table 2 [see Additional file 3]. These findings indicated that aggravated inflammatory responses, lymphopenia, and multiple-organ damage might be correlated with the development of ARDS and subsequently worse clinical outcomes.

Comorbidities, complications, and clinical treatments

Consistent with previous studies, COVID-19 patients with ARDS had an increased risk of developing other serious complications, more patients with ARDS presented with acute liver injury (9.92% vs 1.36%; *P*<0.001), acute kidney injury (18.22% vs 2.31%; *P*<0.001), heart failure (27.89% vs 2.31%; *P*<0.001), cardiac injury (20.40% vs 5.71%; *P*<0.001), and disseminated intravascular coagulation (DIC), 6.91% vs 0.27%; *P*<0.001) (see Additional file 2). Similar results were found in the comparison of non-survivors and survivors in COVID-19 patients with ARDS (see Additional file 3).

In terms of clinical treatments, more patients with ARDS frequently received antibiotic treatment (85.55% vs 65.31%), antiviral therapy (54.52% vs 42.59%), glucocorticoid therapy (63.44% vs 23.95%), and intravenous immunoglobulin therapy (41.33% vs 18.78%; *P*<0.001). Remarkably, patients with ARDS required more clinical oxygen support, including high-flow oxygen ventilation (55.53% vs 41.50%; *P*<0.001) and mechanical ventilation (23.87% vs 2.04%; *P*<0.001) (see Additional file 2). Besides, except for antiviral therapy and high-flow oxygen therapy, all forms of clinical treatments were given more in non-survivors (see Additional file 3).

Risk factors

Multivariate Logistic models were calculated to explore risk factors for development of ARDS and death among COVID-19 patients with adjustment of age, sex, and comorbidities. (Table 3). We observed that elevated inflammatory cytokines were substantially associated with the higher risk for disease progression of ARDS and death in COVID-19 patients, such as IL-6 (OR=1.021, 95%CI=1.016-1.026; *P*<0.001), TNF-α (OR=1.146, 95%CI=1.100-1.194; *P*<0.001), IL-10 (OR=1.126, 95%CI=1.087-1.166; *P*<0.001), and hs-CRP (OR=1.016, 95%CI=1.013-1.019; *P*<0.001). Conversely, the decreased level of counts of immune cell subsets, such as lymphocytes (OR=0.365, 95%CI=0.244-0.545; *P*<0.001), $CD8^+$ T cells (OR=0.983, 95%CI=0.976-0.990; *P*<0.001), $CD3^-CD19^+$ B cells (OR=0.992, 95%CI=0.988-0.997; *P*=0.003) were significantly related to the lower risk of the progression from ARDS to death. Additionally, we found that multiple-organ damage biomarkers, including decreased ALB (OR=0.834, 95%CI=0.799-0.872; *P*<0.001), elevated AST (OR=1.004, 95%CI=1.001-1.007; *P*=0.017), CK-MB (OR=1.350, 95%CI=1.180-1.545; *P*<0.001), creatinine (OR=1.007, 95%CI=1.003-1.012; *P*<0.002), D-Dimer (OR=1.272, 95%CI=1.207-1.340; *P*<0.001) and FDP (OR=1.052, 95%CI=1.038-1.066; *P*<0.001), might associate with high risk of progression of ARDS and outcome of COVID-19 patients.

Comprehensive prediction models

All four predictive score systems, including SOFA, qSOFA, APACHE II and SIRS, performed good prediction capacities for assessing the development risk of ARDS among COVID-19 patients and death risk among patients who developed ARDS. AUCs(95%CI) of SOFA, qSOFA, APACHE II and SIRS scores in assessing the progression of ARDS in COVID-19 patients were 0.857(0.820-0.894), 0.701(0.659-0.744), 0.729(0.679-0.780) and 0.672(0.618-0.725) (Figure 1a). Furthermore, all of them had prominent prediction capacities evaluating death risk. AUCs (95%CI) of SOFA, qSOFA, APACHE II and SIRS scores were 0.853(0.807-0.900), 0.743(0.686-0.799), 0.907(0.870-0.944) and 0.693(0.627-0.758) (Figure 1b).

Furthermore, based on inflammatory-related indexes, multiple-organ damage biomarkers and immune cell subsets, we constructed another three prediction models, all of which were significantly associated with the ARDS development and death. Discrimination of ARDS development risk models was better using multiple-organ damage biomarkers (AUC=0.779, 95%CI=0.746-0.812). The AUCs of inflammatory-related indexes model and immune cell subsets model were 0.729(0.701-0.757) and 0.687(0.629-0.746) (Figure 1a). Conversely, the highest predictive capacities of three prediction models of death was the immune cell

subsets group model (AUC=0.954, 95%CI=0.924-0.985) (Figure 1b). AUCs of multiple-organ damage biomarkers model and inflammatory-related indexes model were 0.927(0.901-0.952), and 0.899(0.874-0.924).

Overall, we established a combined group by integrating four predictive scores, inflammatory-related indexes, immune cell subsets and multiple-organ damage biomarkers. The accuracy of combined score for predicting ARDS development was 0.904(0.866-0.942), and that for the death was 0.959(0.931-0.986). The predictive accuracy of the combined model demonstrated highest among all models in development of ARDS and progression from ARDS to death, indicating that the combined score system is potential of great value in the evaluation of the development and death risk of ARDS in patients with COVID-19 (Figure 1).

Discussion

In this retrospective cohort study, we found that COVID-19 patients with ARDS were more likely to succumb to viral disease Moreover, patients with elevated inflammatory-related indexes, decreased immune cell subsets, abnormal multiple-organ damage biomarkers and higher scores were more likely to develop ARDS and progress from ARDS to death. Specifically, in addition to previously reported risk factors such as neutrophils, IL-6, D-Dimer, leukocytes and platelet, we identified novel risk factors including elevated TNF-α, ALB and CK-MB as well as decreased $CD8^+$ T cell and $CD3^-CD19^+$ B cells. Furthermore, we established a comprehensive risk prediction model by combining risk factors and scores which showed good prediction accuracy for ARDS development (AUC=0.904) and ARDS death risk (AUC=0.959). This model will be beneficial for early identification of development of ARDS and determination of effective treatments in COVID-19 patients.

A total of 796 COVID-19 patients with ARDS were statistically matched by age, sex, and comorbidities to those without ARDS. We noted that patients with ARDS presented excessive inflammation, dysregulated immune response and critical multiple organ damage. Moreover, SOFA, qSOFA, APACHE II and SIRS scores appeared to be higher in COVID-19 patients with ARDS as well as non-survivors. These findings provided supporting evidence that COVID-19 patients with ARDS were associated with higher risk of worse clinical outcomes.

Multivariable logistic regression models were performed to explore risk factors related to ARDS development and death in COVID-19 patients. In terms of inflammatory-related indexes, in addition to previously reported risk factors such as neutrophils, IL-6 and CRP, we found TNF-α was a novel risk factor of ARDS development and death in COVID-19 patients. Cytokine storm has been reported to mediate extensive lung inflammation and ultimately induce ARDS in COVID-19 patients through severe systemic secretion of pro-inflammatory cytokines.[17,18] IL-6 induces various pro-inflammatory cytokines and chemokines through the regulation of STAT3 and activation of the NF-κB pathway, which ultimately causes pneumocyte and endothelial injury, vascular leakage and alveolar edema in cytokine storm.[19-21] During pulmonary infections in COVID-19 patients, intracellular IL-6 acts in concert with CXCL1 and

CXCL2 to recruit polymorphonuclear leukocytes to the lung, resulting in killing pathogens but generating fibrosis.[22] TNF-α, a potential novel risk factor for the development of ARDS identified here, has been reported to mediate airway hyper-responsiveness through the induction of M2 muscarinic receptor dysfunction.[23] In addition, TNF-α not only promotes the apoptosis of both lung epithelial cells and endothelial cells but also inhibits the generation of germinal center B cells by suppressing T cell helper functions. [24,25] An overproduction of TNF-α and IL-6 indicated the exuberant inflammatory responses during course of SARS-COV-2 infection. Collectively, these findings may partly account for the influence of pro-inflammatory cytokines on the high risk of ARDS development and death in COVID-19.

Furthermore, we found that decreased immune cell subsets including T cells, B cells and NK cells, were correlated to the development risk of ARDS among COVID-19 patients and death risk among patients who developed ARDS. Notably, $CD8^+$ T cells and $CD3^-CD19^+$ B cells were identified as novel risk factors. The dysregulated cellular immune responses by decreased lymphocytes are thought to be associated with severity and mortality in COVID-19 patients.[26] $CD8^+$ T cells play a critical role in mediating viral clearance after acute respiratory infections of respiratory syncytial virus, influenza A virus, and human metapneumovirus.[27,28] In addition, $CD8^+$ T cells are reported to suppress inflammatory immune response by secreting immunosuppressive cytokines and cytotoxic enzymes, and the decreased level of $CD8^+$ T cells associated with the dysfunction of immune response and severe complications.[29] $CD3^-CD19^+$ B cells inhibit proinflammatory cytokines and support regulatory T cells differentiation by secreting anti-inflammatory cytokine IL-10.[30] Besides, $CD3^-CD19^+$ B cells act as a booster to the maintenance of immune homeostasis, which are associated with the poor clinical outcomes in patients with autoimmune diseases and viral infectious disease.[31-33]

In addition to elevated inflammatory-related indexes and decreased immune cell subsets, we found abnormal multiple-organ damage biomarkers were other risk factors for development of ARDS and progression from ARDS to death in COVID-19 patients. Previously reported risk factors of COVID-19, such as ALT, AST, hs-cTnI, NT-proBNP, eGFR, D-Dimer and FDP were also confirmed in our study. Furthermore, we identified novel risk factors including CK-MB and ALB. The systemic inflammatory response and immune system disorders during disease progression in patients with COVID-19 result in the high incidence of organ failure symptoms and dysregulated tissue damage biomarkers.[34] Additionally, respiratory dysfunction and hypoxemia in patients with COVID-19 and ARDS caused damage to myocardial cells through the regulation of type 1 and type 2 T helper cells.[35] Moreover, The high serum levels of CK-MB suggested myocardial damage in early-stage which were correlated with the severity and case fatality rate of COVID-19.[36,37] ALB was reported to selectively suppress the expression of pro-inflammatory TNF-α by inhibiting the activation of NF-kB pathway.[38] Additionally, the decreased levels of ALB contribute to inflammatory response and oxidative stress injury through the upregulating the levels of glutathione, which partly accounted for disease severity in MERS patients.[38,39] However, it remains insufficient to explore the association between the multiple-organ damage and the pathogenesis of development of ARDS.

Previous studies have reported that SOFA, qSOFA, APACHE II, and SIRS scoring systems showed good prediction accuracy for evaluating septic shock, multi-organ failure and ICU mortality.[7,8,10-12,40,41] Here, we confirmed that those with higher SOFA, qSOFA, APACHE II or SIRS scores were more likely to develop ARDS and progress to death in COVID-19 patients. Moreover, we found that elevated inflammatory-related indexes, decreased immune cell subsets and abnormal multiple-organ damage biomarkers were associated with ARDS development and progression from ARDS to death in COVID-19 patients. In addition, the patients with increased levels of the biomarkers were more likely to develop complications such as heart failure, acute cardiac, kidney, liver injury and DIC. Therefore, the combined model integrating risk factors and scores showed the best predictive capacities of both development of ARDS and progression from ARDS to death in COVID-19 patients.

It is critical to recommend standardized and effective treatment protocols for SARS-COV-2 infection worldwide to improve poor clinical outcomes. Consistent with other studies, antibiotics and antivirals were widely used in COVID-19 treatment.[13,42] Notably, COVID-19 patients with ARDS received more supportive therapy, such as ventilation treatments and glucocorticoid therapy. Preliminary evidence suggested the standard supportive care for ARDS patients was a protective ventilatory strategy, which might improve prognoses of patients with ARDS.[43,44] Additionally, recent studies showed that corticosteroids could be an effective treatment. The administration of dexamethasone and methylprednisolone could decrease duration of mechanical ventilation and reduce the death risk of patients with COVID-19 who develop ARDS.[45,46] In view of the excessive inflammation, dysregulated immune response and multiple organ damage in COVID-19 patients with ARDS, the current management of COVID-19 should be focused on inflammatory immune response, treatment of complications and supportive care, especially oxygen support.

Based on our study, several management strategies are warranted for COVID-19 patients with ARDS. First, inflammatory-related indexes and organ damage indexes should be monitored at different stages to prevent the development of ARDS in COVID-19 patients. Second, early application of systemic immune modulators such as intravenous immunoglobulin should be considered to reduce aberrant immune responses at the early stage of ARDS, which is helpful to prevent the progression of ARDS.[47] Third, Supportive therapy such as ventilation treatment is also critical for COVID-19 patients with ARDS.

Our study has several limitations. First, this was a retrospective cohort study and not all laboratory tests were done in all patients. The missing data might affect the interpretation of the results. Second, the potential mechanisms of multiple organ damage and ARDS development and progression to death need to be further investigated and confirmed. Third, our study was performed in a single-center hospital, which needs to be further confirmed in multi-center studies in the future. Finally, given that age and comorbidities, such as diabetes and hypertension, have been reported as the common risk factors of COVID-19 with ARDS, these factors were statistically matched between patients with ARDS and those without ARDS and were not included in this study.

Conclusion

In summary, we found higher SOFA, qSOFA, APACHE II and SIRS scores, elevated inflammatory-indexes, decreased immune cell subsets and abnormal multiple-organ damage biomarkers related to higher death risk of COVID-19 with ARDS. Furthermore, we integrated aforementioned scores and risk factors to establish a comprehensive risk prediction model for COVID-19 patients with ARDS, showing a good prediction capacity and help to establish protective measures for ARDS development and death.

Abbreviations

COVID-19, Corona virus disease 2019; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; ARDS, acute respiratory distress syndrome; RT-PCR, Real-time reverse transcriptase polymerase chain reaction; SOFA, Sequential organ failure assessment; qSOFA, quick SOFA; APACHE II, The acute physiology and chronic health evaluation II; SIRS, The systemic inflammatory response syndrome; hs-CRP, High-sensitivity C-reactive protein; hs-cTnI, Hypersensitive cardiac troponin I; MERS, Middle East Respiratory Syndrome;

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tongji Hospital Tongji Medical College, HUST. l. Individual informed consent was waived by the ethics committee listed above because this study used currently existing sample collected during course of routine medical care and did not pose any additional risks to the patients.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

JQ, JT, and ZW were the overall principal investigators in this study who conceived the study and obtained financial support, were responsible for the study design, and supervised the entire study. ZY, TD, YW, SN, QL and CL recruited participants. JW, LW, MJ, ZL, JX, and YL drafted the paper. LW, MJ, and ZL completed the statistical analyses. JX and YL completed data analysis, interpreted the results. JQ, JT and ZW reviewed the manuscript. All authors participated in interpretation data, manuscript writing, and review of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic, clinical, radiographic, laboratory findings of ARDS and non-ARDS patients with COVID-19

Indicators	Total		ARDS		Non-ARDS	*P*value
Characteristics	**N = 1531**		**N = 796**		**N = 735**	
Age, years	60.00(51.00-68.00)		61.00(51.00-68.00)		60.00(50.00-68.00)	0.091
Sex						
Male	833(54.41%)		445(55.90%)		388(52.79%)	0.221
Female	698(45.59%)		351(44.10%)		347(47.21%)	
Comorbidities	**N = 1531**		**N = 796**		**N = 735**	
Hypertension	454(29.65%)		252(31.66%)		202(27.48%)	0.074
Diabetes	202(13.19%)		108(13.57%)		94(12.79%)	0.653
Coronary heart disease	99(6.47%)		58(7.29%)		41(5.58%)	0.175
Chronic obstructive pulmonary disease	9(0.59%)		7(0.88%)		2(0.27%)	0.223
Hepatitis	28(1.83%)		19(2.39%)		9(1.22%)	0.090
Pulmonary tuberculosis	26(1.70%)		16(2.01%)		10(1.36%)	0.326
Chronic bronchitis	21(1.37%)		12(1.51%)		9(1.22%)	0.634
Initial symptoms	**N = 1408**		**N = 740**		**N = 668**	
Fever	1036(73.58%)		627(84.73%)		409(61.23%)	<0.001*
Cough	943(66.97%)		485(65.54%)		458(68.56%)	0.229
Expectoration	584(41.48%)		273(36.89%)		311(46.56%)	<0.001*
Dyspnea	560(39.77%)		322(43.51%)		238(35.63%)	0.003*
Fatigue	234(16.62%)		139(18.78%)		95(14.22%)	0.022*
Chest tightness	217(15.41%)		125(16.89%)		92(13.77%)	0.105
Diarrhea	308(21.88%)		173(23.38%)		135(20.21%)	0.151
Headache	95(6.75%)		57(7.70%)		38(5.69%)	0.132
Myalgia	126(8.95%)		76(10.27%)		50(7.49%)	0.068
Anorexia	106(7.53%)		60(8.11%)		46(6.89%)	0.386
Vertigo	52(3.69%)		37(5.00%)		15(2.25%)	0.006*
Chills	148(10.51%)		82(11.08%)		66(9.88%)	0.463
CT findings	**N = 1275**		**N = 577**		**N = 698**	
Ground-glass opacity	621(48.71%)		293(50.78%)		328(46.99%)	0.178
Patchy shadows	975(76.47%)		449(77.82%)		526(75.36%)	0.303
Fibrous stripes	471(36.94%)		189(32.76%)		282(40.40%)	0.005*
Pleural thickening	285(22.35%)		158(27.38%)		127(18.19%)	<0.001*
Nodules	126(9.88%)		47(8.15%)		79(11.32%)	0.059
Lymphadenia	263(20.63%)		132(22.88%)		131(18.77%)	0.071
Bilateral pulmonary	1204(94.43%)		555(96.19%)		649(92.98%)	0.013*
Right lung	34(2.67%)		9(1.56%)		25(3.58%)	0.026*
Left lung	35(2.75%)		12(2.08%)		23(3.30%)	0.186
Laboratory examinations						
Blood routine						
Leukocytes count (N = 1531), ×10^9/L	5.77(4.50-7.77)	N = 796	6.13(4.64-8.94)	N = 735	5.51(4.40-7.08)	<0.001*
Erythrocytes count (N = 1531), ×10^12/L	4.22(3.81-4.62)	N = 796	4.22(3.74-4.62)	N = 735	4.21(3.84-4.62)	0.294
Neutrophils count (N = 1531), ×10^9/L	3.91(2.66-5.67)	N = 796	4.40(2.88-7.42)	N = 735	3.48(2.50-4.67)	<0.001*
Eosinophils count (N = 1531), ×10^9/L	0.02(0.00-0.08)	N = 796	0.01(0.00-0.05)	N = 735	0.06(0.01-0.11)	<0.001*
Basophils count (N = 1531), ×10^9/L	0.01(0.01-0.02)	N = 796	0.01(0.00-0.02)	N = 735	0.02(0.01-0.03)	<0.001*
Immune cell subsets						
Lymphocytes count (N = 1531), ×10^9/L	1.11(0.73-1.57)	N = 796	0.88(0.60-1.28)	N = 735	1.35(0.98-1.79)	<0.001*
$CD3^+CD19^-$ T cells count (N = 332), /μL	1005.50(672.75-1304.00)	N = 159	845.00(362.50-1247.00)	N = 173	1073.00(849.00-1361.00)	<0.001*
$CD8^+$ T cells count (N = 332), /μL	329.50(207.50-430.25)	N = 159	279.00(103.50-408.00)	N = 173	344.00(262.00-446.00)	<0.001*
$CD3^-CD19^+$ B cells count (N =	176.50(115.50-	N =	152.00(76.00-	N =	184.00(135.00-	0.002*

332), /μL	251.25)	159	238.00)	173	261.00)	
CD3-CD16^{+}CD56^{+} NK cells count (N = 332), /μL	160.50(100.00-260.50)	N = 159	138.00(55.00-235.00)	N = 173	192.00(125.00-282.00)	<0.001*
T cells+ B cells+ NK cells count (N = 332), /μL	1401.50(956.75-1827.00)	N = 159	1194.00(646.50-1689.50)	N = 173	1545.00(1245.00-1874.00)	<0.001*
Inflammatory cytokines and biomarkers						
IL-6 (N = 1260), pg/mL	5.33(2.01-26.42)	N = 646	13.24(3.09-50.04)	N = 614	3.11(1.62-9.12)	<0.001*
IL-10 (N = 1232), pg/mL	5.00(5.00-6.80)	N = 632	5.00(5.00-9.85)	N = 600	5.00(5.00-5.00)	<0.001*
IL-8 (N = 1233), pg/mL	11.50(6.90-22.20)	N = 633	13.80(7.90-27.70)	N = 600	9.30(5.95-16.63)	<0.001*
TNF-α (N = 1263), pg/mL	7.70(5.80-10.40)	N = 642	8.30(6.13-11.40)	N = 621	7.30(5.30-9.50)	<0.001*
IL-1β (N = 1232), pg/mL	5.00(5.00-5.00)	N = 632	5.00(5.00-5.00)	N = 600	5.00(5.00-5.00)	0.277
IL-2R (N = 1226), U/mL	529.00(345.00-844.00)	N = 631	658.00(410.50-1075.00)	N = 595	441.00(303.00-645.50)	<0.001*
hs-CRP (N = 1497), mg/L	20.70(2.50-72.00)	N = 789	47.80(10.10-105.80)	N = 708	5.20(1.20-33.35)	<0.001*
Organ damage indexes						
ALT (N = 1527), U/L	22.00(15.00-39.00)	N = 796	24.00(16.00-41.00)	N = 731	21.00(14.00-37.00)	0.001*
AST (N = 1527), U/L	26.00(19.00-39.00)	N = 796	31.00(21.00-48.00)	N = 731	23.00(18.00-31.00)	<0.001*
GGT (N = 1525), U/L	29.00(19.00-51.00)	N = 795	33.00(20.00-58.00)	N = 730	27.00(18.00-44.00)	<0.001*
ALB (N = 1524), g/L	36.00(32.08-40.40)	N = 794	34.30(30.20-37.88)	N = 730	38.60(34.43-42.00)	<0.001*
GLO (N = 1524), g/L	32.35(28.80-35.90)	N = 794	33.80(30.23-37.10)	N = 730	30.60(27.63-34.00)	<0.001*
TBIL (N = 1531), μmol/L	9.10(6.60-12.60)	N = 796	9.80(7.00-13.80)	N = 735	8.30(6.30-11.50)	<0.001*
BUN (N = 1523), mmol/L	4.60(3.50-6.10)	N = 794	4.90(3.40-7.40)	N = 729	4.40(3.60-5.40)	<0.001*
LDH (N = 1443), U/L	259.00(200.00-375.50)	N = 767	323.00(232.00-484.50)	N = 676	220.00(187.00-279.00)	<0.001*
eGFR (N = 1522), ml/(min*1.73m^2)	92.90(79.03-103.40)	N = 792	91.95(72.98-103.73)	N = 730	94.15(83.73-103.08)	0.002*
Creatinine (N = 1531), μmol/L	70.00(58.00-86.00)	N = 796	72.50(57.00-92.00)	N = 735	70.00(59.00-81.00)	0.009*
NT-proBNP (N = 1240), pg/mL	106.00(35.00-365.25)	N= 656	186.50(60.00-816.50)	N = 584	62.00(25.00-156.25)	<0.001*
ALP (N = 1444), U/L	67.00(56.00-82.00)	N = 770	69.00(55.00-88.00)	N = 674	66.00(56.00-78.00)	0.004*
CK (N = 1012), U/L	68.00(43.75-118.00)	N = 533	74.00(43.00-153.00)	N = 479	63.00(44.00-94.00)	<0.001*
CK-MB (N = 1002), U/L	0.70(0.40-1.30)	N = 471	0.80(0.40-2.10)	N = 531	0.70(0.40-1.10)	<0.001*
hs-cTnI (N =1361), pg/mL	3.80(1.90-11.10)	N = 713	5.70(2.40-20.00)	N = 648	2.70(1.90-5.83)	<0.001*
Platelet count (N = 1531), ×10^9/L	210.00(159.00-273.00)	N = 796	194.00(144.00-254.00)	N = 735	225.00(178.00-282.00)	<0.001*
TT (N = 654), s	16.70(15.80-17.70)	N = 398	16.75(15.70-18.10)	N = 256	16.50(15.90-17.30)	0.040*
PT (N = 1513), s	13.80(13.20-14.50)	N = 791	14.00(13.40-15.10)	N = 722	13.60(13.20-14.10)	<0.001*
APTT (N = 1432), s	38.90(35.90-42.70)	N = 733	39.30(36.00-43.70)	N = 699	38.30(35.80-41.70)	0.001*
D-Dimer (N =1497), ug/mL	0.64(0.32-1.77)	N = 781	1.12(0.48-2.89)	N = 716	0.43(0.22-0.88)	<0.001*
FDP (N = 1104), g/L	4.00(4.00-7.30)	N = 564	5.20(4.00-18.05)	N = 540	4.00(4.00-4.00)	<0.001*
Score prediction						
SOFA score	3.00(3.00-4.00)	N = 233	3.00(2.00-5.00)	N = 140	2(1.00-2.00)	<0.001*

qSOFA score	0.00(0.00-1.00)	N = 233	1.00(0.00-1.00)	N = 140	0(0.00-0.00)	<0.001*
APACHE II score	10.00(6.00-15.50)	N = 233	13.00(8.00-17.50)	N = 140	7.00(4.00-10.00)	<0.001*
SIRS score	1.00(0.00-2.00)	N = 233	2.00(1.00-2.00)	N = 140	1.00(0.00-2.00)	<0.001*
ICU admission	**N = 1503**		**N = 785**		**N = 718**	
ICU	154(10.25%)		151(19.24%)		3(0.42%)	<0.001*
Non-ICU	1349(89.75%)		634(80.76%)		715(99.58%)	
Outcomes	**N = 1531**		**N = 796**		**N = 735**	
Survivor	1250(81.65%)		524(65.83%)		726(98.78%)	<0.001*
Non-survivor	281(18.35%)		272(34.17%)		9(1.22%)	

Abbreviation: COVID-19, Corona virus disease 2019; CT, Computerized tomography; CD, Cluster of differentiation; NK cells, Natural killer cells; IL-6, Interleukin 6; IL-10, Interleukin 10; IL-8, Interleukin 8; TNF-α, Tumor necrosis factor α; IL-1β, Interleukin 1β; IL-2R, Interleukin 2 receptor; hs-CRP, High-sensitivity C-reactive protein; ALT, Glutamic-pyruvic transaminase; AST, Glutamic-oxaloacetic transaminase; GGT, Gamma-glutamyl transpeptidase; ALB, Albumin; GLO, Globulin; TBIL, Total bilirubin; BUN, Blood urea nitrogen; LDH, Lactic dehydrogenase; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; ALP, Alkaline phosphatase; CK, Creatine kinase; CK-MB, Creatine kinase-MB; hs-cTnI, Hypersensitive cardiac troponin I; TT, Thrombin time; PT, Prothrombin time; APTT, activated partial thromboplastin time; FDP, Fibrinogen degradation products; SOFA, Sequential organ failure assessment; qSOFA, quick SOFA; APACHE II, The acute physiology and chronic health evaluation II; SIRS, The systemic inflammatory response syndrome; ECMO, extracorporeal membrane oxygenation; IQR, Interquartile range; SD, standard deviation. Continuous variables were described as median (IQR) or mean and standard deviation (SD). *P* values were calculated by Mann-Whitney U non-parameter test for skewed distributed data or Student's t-test for normal distributed data (b). Categorical variables were expressed as number (%). *P* values were calculated by Pearson χ^2 test. $^*P < 0.05$.

Table 2. Demographic, clinical, radiographic, laboratory findings of non-survivors and survivors COVID-19 patients with ARDS

Indicators	Total		non-survivors		survivors	*P*value
Characteristics	**N = 796**		**N = 272**		**N = 524**	
Age, years	61.00(51.00-68.00)		69.00(62.00-77.00)		56.00(46.00-64.00)	<0.001*
Sex						
Male	445(55.90%)		187(68.80%)		258(49.20%)	<0.001*
Female	351(44.10%)		85(31.30%)		266(50.80%)	
Comorbidities	**N = 796**		**N = 272**		**N = 524**	
Hypertension	252(31.70%)		106(39.00%)		146(27.90%)	0.001*
Diabetes	108(13.60%)		38(14.00%)		70(13.40%)	0.811
Coronary heart disease	58(7.30%)		32(11.80%)		26(5.00%)	<0.001*
Chronic obstructive pulmonary disease	7(0.90%)		4(1.50%)		3(0.60%)	0.375
Hepatitis	19(2.40%)		7(2.60%)		12(2.30%)	0.804
Pulmonary tuberculosis	16(2.00%)		9(3.30%)		7(1.30%)	0.060
Chronic bronchitis	12(1.50%)		8(2.90%)		4(0.80%)	0.037*
Initial symptoms	**N = 796**		**N = 272**		**N = 524**	
Fever	627(84.73%)		222(89.52%)		405(82.32%)	0.010*
Cough	485(65.50%)		157(63.30%)		328(66.70%)	0.364
Expectoration	273(36.90%)		103(41.50%)		170(34.60%)	0.063
Dyspnea	322(43.50%)		124(50.00%)		198(40.20%)	0.012*
Fatigue	139(18.80%)		49(19.80%)		90(18.30%)	0.630
Chest tightness	125(16.90%)		40(16.10%)		85(17.30%)	0.694
Diarrhea	173(23.40%)		59(23.80%)		114(23.20%)	0.851
Headache	57(7.70%)		11(4.40%)		46(9.30%)	0.018*
Myalgia	76(10.30%)		14(5.60%)		62(12.60%)	0.003*
Anorexia	60(8.10%)		21(8.50%)		39(7.90%)	0.799
Vertigo	37(5.00%)		18(7.30%)		19(3.90%)	0.045*
Chills	82(11.10%)		23(9.30%)		59(12.00%)	0.266
CT findings	**N = 577**		**N = 57**		**N = 520**	
Ground-glass opacity	293(50.80%)		31(54.40%)		262(50.40%)	0.566
Patchy shadows	449(77.80%)		41(71.90%)		408(78.50%)	0.260
Fibrous stripes	189(32.80%)		9(15.80%)		180(34.60%)	0.004*
Pleural thickening	158(27.40%)		24(42.10%)		134(25.80%)	0.009*
Nodules	47(8.10%)		5(8.80%)		42(8.10%)	1.000
Lymphadenia	132(22.90%)		22(38.60%)		110(21.20%)	0.003*
Bilateral pulmonary	555(96.20%)		57(100.00%)		498(95.80%)	0.223
Right lung	9(1.60%)		0(0.00%)		9(1.70%)	0.610[a]
Left lung	12(2.10%)		0(0.00%)		12(2.30%)	0.503
Laboratory examinations						
Blood routine						
Leukocytes count (N = 796), ×10^9/L	6.13(4.63-8.95)	N = 272	9.06(6.01-13.10)	N = 524	5.37(4.27-7.09)	<0.001*
Erythrocytes count (N =796), ×10^12/L	4.22(3.74-4.62)	N = 272	4.17(3.58-4.63)	N = 524	4.25(3.83-4.62)	0.013*
Neutrophils count (N = 796), ×10^9/L	4.40(2.88-7.42)	N = 272	7.87(4.51-11.83)	N = 524	3.77(2.64-5.28)	<0.001*
Eosinophils count (N = 796), ×10^9/L	0.01(0.00-0.05)	N = 272	0.00(0.00-0.01)	N = 524	0.02(0.00-0.07)	<0.001*
Basophils count (N = 796), ×10^9/L	0.01(0.00-0.02)	N = 272	0.01(0.00-0.02)	N = 524	0.01(0.00-0.02)	0.727
Immune cell subsets						
Lymphocytes count (N = 796),	0.88(0.60-1.28)	N =	0.63(0.43-0.85)	N =	1.07(0.74-1.45)	<0.001*

×10^9/L		272		524		
$CD3^+CD19^-$ T cells count (N = 159), /μL	845.00(359.00-1252.00)	N = 53	279.00(135.50-417.50)	N = 106	1082.00(800.00-1405.25)	<0.001*
$CD8^+$ T cells count (N = 159), /μL	279.00(103.00-408.00)	N = 53	63.00(29.50-130.50)	N = 106	365.00(267.25-494.75)	<0.001*
$CD3^-CD19^+$ B cells count (N = 159), /μL	152.00(75.00-239.00)	N = 53	75.00(40.00-148.50)	N = 106	183.00(124.00-274.50)	<0.001*
$CD3^-CD16^+CD56^+$ NK cells count (N = 159), /μL	138.00(55.00-238.00)	N = 53	35.00(15.50-76.50)	N = 106	181.00(125.00-288.50)	<0.001*
T cells+ B cells+ NK cells count (N = 159), /μL	1194.00(634.00-1709.00)	N = 53	424.00(272.50-703.00)	N = 106	1466.50(1189.50-1922.25)	<0.001*
Inflammatory cytokines and biomarkers						
IL-6(N = 646), pg/mL	13.24(3.08-50.05)	N = 195	61.60(29.22-153.10)	N = 451	5.20(2.08-21.12)	<0.001*
IL-10(N = 632), pg/mL	5.00(5.00-9.95)	N = 191	10.30(6.30-18.70)	N = 441	5.00(5.00-6.20)	<0.001*
IL-8(N = 633), pg/mL	13.80(7.90-27.85)	N = 192	28.75(16.48-62.88)	N = 441	10.40(6.65-18.40)	<0.001*
TNF-α (N = 642), pg/mL	8.30(6.10-11.40)	N = 192	11.55(8.23-17.25)	N = 450	7.55(5.60-9.80)	<0.001*
IL-1β (N = 632), pg/mL	5.00(5.00-5.00)	N = 192	5.00(5.00-7.08)	N = 440	5.00(5.00-5.00)	<0.001*
IL-2R (N = 631), U/mL	658.00(409.00-1077.00)	N = 190	1148.00(726.75-1634.00)	N = 441	538.00(358.00-813.00)	<0.001*
hs-CRP (N = 789), mg/L	47.80(10.10-106.15)	N = 267	105.80(59.60-164.40)	N = 522	23.75(3.90-68.65)	<0.001*
Organ damage indexes						
ALT (N = 796), U/L	24.00(16.00-41.00)	N = 272	27.00(18.00-42.00)	N = 524	23.00(15.00-40.00)	0.013*
AST (N = 796), U/L	31.00(21.00-48.00)	N = 272	41.00(28.25-59.00)	N = 524	26.00(19.00-38.00)	<0.001*
GGT (N = 795), U/L	33.00(20.00-58.00)	N = 272	39.00(24.25-70.00)	N = 523	30.00(19.00-52.00)	<0.001*
ALB (N = 794), g/L	34.24±5.59	N = 271	30.76±4.79	N = 523	36.04±5.10	<0.001*,[b]
GLO (N = 794), g/L	33.80(30.20-37.13)	N = 271	35.70(31.50-39.20)	N = 523	32.90(29.80-36.00)	<0.001*
TBIL (N = 796), μmol/L	9.80(7.00-13.80)	N = 272	12.40(9.03-18.80)	N = 524	8.70(6.40-11.70)	<0.001*
BUN (N = 794), mmol/L	4.90(3.40-7.43)	N = 270	8.30(5.60-13.08)	N = 524	4.05(3.10-5.40)	<0.001*
LDH (N = 767), U/L	323.00(232.00-485.00)	N = 268	504.50(366.00-670.50)	N = 499	268.00(206.00-366.00)	<0.001*
eGFR (N = 792), ml/(min*1.73m^2)	91.95(72.93-103.78)	N = 269	72.70(47.95-90.95)	N = 523	97.00(86.00-106.50)	<0.001*
Creatinine (N = 796), μmol/L	72.50(57.00-92.00)	N = 272	87.00(67.00-114.00)	N = 524	66.00(55.00-83.00)	<0.001*
NT-proBNP (N = 656), pg/mL	186.50(60.00-819.50)	N = 244	888.50(367.25-2602.50)	N = 412	86.50(34.25-219.50)	<0.001*
ALP (N = 770), U/L	69.00(55.00-88.25)	N = 272	78.50(62.00-109.00)	N = 498	65.00(54.00-80.00)	<0.001*
CK (N = 533), U/L	74.00(43.00-154.00)	N = 187	128.00(69.00-335.00)	N = 346	61.00(37.00-106.25)	<0.001*
CK-MB (N = 471), U/L	0.80(0.40-2.10)	N = 168	2.45(1.20-5.95)	N = 303	0.60(0.30-0.90)	<0.001*
hs-cTnI (N = 713), pg/mL	5.70(2.40-20.15)	N = 252	35.90(11.20-201.98)	N = 461	3.30(1.90-6.40)	<0.001*
Platelet count (N = 796), ×10^9/L	194.00(144.00-254.00)	N = 272	159.00(107.25-222.75)	N = 524	207.50(160.00-276.50)	<0.001*
TT (N = 398), s	16.75(15.70-18.13)	N = 239	17.00(15.80-19.20)	N = 159	16.40(15.60-17.20)	<0.001*
PT (N = 791), s	14.00(13.40-15.10)	N = 272	15.35(14.30-17.10)	N = 519	13.70(13.10-14.30)	<0.001*
APTT (N = 733), s	39.30(36.00-43.70)	N = 241	40.10(36.10-46.20)	N = 492	39.10(36.00-42.80)	0.006*

D-Dimer (N = 781), ug/mL	1.12(0.48-2.89)	N = 266	4.29(1.48-16.20)	N = 515	0.64(0.37-1.40)	<0.001*
FDP (N = 564), g/L	5.20(4.00-18.15)	N = 206	26.10(7.40-89.25)	N = 358	4.00(4.00-5.83)	<0.001*
Score prediction						
SOFA score (N = 233)	3.00(2.00-5.00)	N = 118	4.00(3.00-6.00)	N = 115	2.00(2.00-3.00)	<0.001*
qSOFA score (N = 233)	1.00(0.00-1.00)	N = 118	1.00(1.00-1.00)	N = 115	0.00(0.00-1.00)	<0.001*
APACHE II score (N = 233)	13.00(8.00-17.50)	N = 118	17.00(14.00-20.25)	N = 115	8.00(5.00-11.00)	<0.001*
SIRS score (N = 233)	2.00(1.00-2.00)	N = 118	2.00(1.00-2.00)	N = 115	1.00(0.00-2.00)	<0.001*
ICU	**N = 785**		**N = 272**		**N = 513**	
ICU	151(19.20%)		145(53.30%)		6(1.20%)	<0.001*
Non-ICU	634(80.80%)		127(46.70%)		507(98.80%)	

Abbreviation: COVID-19, Corona virus disease 2019; CT, Computerized tomography; CD, Cluster of differentiation; NK cells, Natural killer cells; IL-6, Interleukin 6; IL-10, Interleukin 10; IL-8, Interleukin 8; TNF-α, Tumor necrosis factor α; IL-1β, Interleukin 1β; IL-2R, Interleukin 2 receptor; hs-CRP, High-sensitivity C-reactive protein; ALT, Glutamic-pyruvic transaminase; AST, Glutamic-oxaloacetic transaminase; GGT, Gamma-glutamyl transpeptidase; ALB, Albumin; GLO, Globulin; TBIL, Total bilirubin; BUN, Blood urea nitrogen; LDH, Lactic dehydrogenase; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; ALP, Alkaline phosphatase; CK, Creatine kinase; CK-MB, Creatine kinase-MB; hs-cTnI, Hypersensitive cardiac troponin I; TT, Thrombin time; PT, Prothrombin time; APTT, activated partial thromboplastin time; FDP, Fibrinogen degradation products; SOFA, Sequential organ failure assessment; qSOFA, quick SOFA; APACHE II, The acute physiology and chronic health evaluation II; SIRS, The systemic inflammatory response syndrome; ECMO, extracorporeal membrane oxygenation; IQR, Interquartile range; SD, standard deviation. Continuous variables were described as median (IQR) or mean and standard deviation (SD). *P* values were calculated by Mann-Whitney U non-parameter test for skewed distributed data or Student's t-test for normal distributed data (b). Categorical variables were expressed as number (%). *P* values were calculated by Pearson χ^2 test or Fisher's exact test (a). $^*P < 0.05$.

Table 3 Risk Factors Associated with ARDS Development or Progression from ARDS to Death

Indicators	ARDS				Death			
	Univariable logistic regression		Multivariable logistic regression		Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	*P* value	OR (95% CI)	*P value*$^{\beta}$	OR (95% CI)	*P* value	OR (95% CI)	*P value*$^{\beta}$
Laboratory examinations								
Blood routine								
Leukocytes count, ×10^9/L	1.154(1.113-1.196)	<0.001*	1.148(1.107-1.190)	<0.001*	1.316(1.252-1.384)	<0.001*	1.288(1.216-1.364)	<0.001*
Erythrocytes count, ×10^12/L	0.862(0.741-1.002)	0.053	0.850(0.719-1.005)	0.057	0.680(0.551-0.839)	<0.001*	0.600(0.458-0.786)	<0.001*
Monocytes count, ×10^9/L	1.012(0.930-1.100)	0.786	1.017(0.936-1.104)	0.696	1.080(0.900-1.296)	0.408	1.162(1.010-1.336)	0.036*
Neutrophils count, ×10^9/L	1.250(1.198-1.305)	<0.001*	1.249(1.195-1.305)	<0.001*	1.393(1.318-1.473)	<0.001*	1.349(1.269-1.435)	<0.001*
Eosinophils count, ×10^9/L	0.001(0.000-0.007)	<0.001*	0.002(0.000-0.007)	<0.001*	0.001(0.000-0.021)	<0.001*	0.004(0.000-0.115)	0.001*
Immune cell subsets								
Lymphocytes count, ×10^9/L	0.333(0.275-0.402)	<0.001*	0.326(0.267-0.398)	<0.001*	0.202(0.139-0.293)	<0.001*	0.365(0.244-0.545)	<0.001*
$CD3^+CD19^-$ T cells count, /μL	0.999(0.998-0.999)	<0.001*	0.999(0.998-0.999)	<0.001*	0.993(0.991-0.995)	<0.001*	0.994(0.991-0.996)	<0.001*
$CD8^+$ T cells count, /μL	0.998(0.996-0.999)	<0.001*	0.998(0.996-0.999)	0.001*	0.983(0.978-0.988)	<0.001*	0.983(0.976-0.990)	<0.001*
$CD3^-CD19^+$ B cells count, /μL	0.998(0.996-0.999)	0.012*	0.998(0.996-1.000)	0.045*	0.991(0.987-0.995)	<0.001*	0.992(0.988-0.997)	0.003*
$CD3^-CD16^+CD56$+ NK cells count, /μL	0.996(0.994-0.998)	<0.001*	0.996(0.994-0.998)	<0.001*	0.981(0.974-0.987)	<0.001*	0.982(0.975-0.990)	<0.001*
T cells+ B cells+ NK cells count, /μL	0.999(0.999-0.999)	<0.001*	0.999(0.998-0.999)	<0.001*	0.995(0.993-0.996)	<0.001*	0.995(0.993-0.997)	<0.001*
Inflammatory cytokines and biomarkers								
IL-6, pg/mL	1.020(1.015-1.025)	<0.001*	1.021(1.016-1.026)	<0.001*	1.025(1.020-1.031)	<0.001*	1.021(1.016-1.026)	<0.001*
IL-10, pg/mL	1.073(1.045-1.101)	<0.001*	1.070(1.043-1.098)	<0.001*	1.146(1.107-1.186)	<0.001*	1.126(1.087-1.166)	<0.001*
IL-8, pg/mL	1.000(1.000-1.000)	0.958	1.000(1.000-1.000)	0.946	1.007(1.003-1.010)	<0.001*	1.003(1.000-1.005)	0.027*
TNF-α, pg/mL	1.076(1.050-1.102)	<0.001*	1.075(1.048-1.102)	<0.001*	1.187(1.140-1.236)	<0.001*	1.146(1.100-1.194)	<0.001*
IL-1β, pg/mL	0.996(0.983-1.009)	0.556	0.995(0.982-1.009)	0.498	1.041(1.011-1.073)	0.008*	1.052(1.025-1.081)	<0.001*
IL-2R, U/mL	1.002(1.001-1.002)	<0.001*	1.002(1.001-1.002)	<0.001*	1.002(1.002-1.002)	<0.001*	1.002(1.001-1.002)	<0.001*
hs-CRP, mg/L	1.016(1.013-1.019)	<0.001*	1.017(1.014-1.020)	<0.001*	1.018(1.015-1.021)	<0.001*	1.016(1.013-1.019)	<0.001*
Organ damage indexes								
ALT, U/L	1.004(1.002-1.007)	0.002*	1.004(1.002-1.007)	0.003*	1.002(1.000-1.003)	0.113	1.001(0.999-1.004)	0.283
AST, U/L	1.021(1.016-1.027)	<0.001*	1.021(1.015-1.027)	<0.001*	1.006(1.003-1.010)	0.001*	1.004(1.001-1.007)	0.017*
GGT, U/L	1.004(1.002-1.006)	<0.001*	1.004(1.002-1.006)	<0.001*	1.002(1.000-1.004)	0.031*	1.002(1.000-1.004)	0.064
ALB, g/L	0.871(0.853-0.890)	<0.001*	0.858(0.838-0.878)	<0.001*	0.803(0.772-0.834)	<0.001*	0.834(0.799-0.872)	<0.001*
GLO, g/L	1.095(1.073-	<0.001*	1.094(1.072-	<0.001*	1.074(1.045-	<0.001*	1.043(1.010-	0.009*

	1.117)		1.117)		1.103)		1.076)	
BUN, mmol/L	1.149(1.107-1.192)	<0.001*	1.160(1.112-1.209)	<0.001*	1.535(1.429-1.650)	<0.001*	1.369(1.268-1.478)	<0.001*
LDH, U/L	1.008(1.007-1.009)	<0.001*	1.008(1.007-1.009)	<0.001*	1.008(1.007-1.009)	<0.001*	1.007(1.006-1.009)	<0.001*
eGFR, ml/(min*1.73m^2	0.989(0.984-0.993)	<0.001*	0.989(0.983-0.994)	<0.001*	0.958(0.951-0.965)	<0.001*	0.974(0.966-0.982)	<0.001*
Creatinine, μmol/L	1.003(1.001-1.006)	0.007*	1.003(1.000-1.005)	0.024*	1.018(1.013-1.024)	<0.001*	1.007(1.003-1.012)	0.002*
NT-proBNP, pg/mL	1.001(1.001-1.001)	<0.001*	1.001(1.001-1.002)	<0.001*	1.001(1.000-1.001)	<0.001*	1.000(1.000-1.000)	<0.001*
CK, U/L	1.004(1.002-1.005)	<0.001*	1.003(1.002-1.005)	<0.001*	1.003(1.002-1.004)	<0.001*	1.003(1.002-1.005)	<0.001*
CK-MB, U/L	1.228(1.129-1.337)	<0.001*	1.205(1.106-1.314)	<0.001*	1.714(1.472-1.997)	<0.001*	1.350(1.180-1.545)	<0.001*
hs-cTnI, pg/mL	1.010(1.006-1.015)	<0.001*	1.010(1.006-1.014)	<0.001*	1.001(1.000-1.001)	0.002*	1.000(1.000-1.001)	0.029*
Platelet count, ×10^9/L	0.997(0.995-0.998)	<0.001*	0.997(0.996-0.998)	<0.001*	0.993(0.991-0.995)	<0.001*	0.995(0.992-0.997)	<0.001*
PT, s	1.536(1.396-1.691)	<0.001*	1.545(1.396-1.710)	<0.001*	2.359(2.033-2.738)	<0.001*	2.118(1.800-2.492)	<0.001*
APTT, s	1.036(1.019-1.054)	<0.001*	1.035(1.017-1.054)	0.00012*	1.055(1.032-1.080)	<0.001*	1.057(1.028-1.087)	<0.001*
D-Dimer, ug/mL	1.415(1.303-1.536)	<0.001*	1.438(1.318-1.568)	<0.001*	1.305(1.237-1.377)	<0.001*	1.272(1.207-1.340)	<0.001*
FDP, g/L	1.053(1.037-1.070)	<0.001*	1.055(1.038-1.072)	<0.001*	1.063(1.047-1.079)	<0.001*	1.052(1.038-1.066)	<0.001*
Score prediction								
SOFA score	3.598(2.696-4.802)	<0.001*	4.035(2.917-5.581)	<0.001*	3.342(2.413-4.630)	<0.001*	3.087(2.137-4.460)	<0.001*
qSOFA score	6.482(3.829-10.974)	<0.001*	5.966(3.473-10.249)	<0.001*	6.394(3.702-11.044)	<0.001*	8.372(4.179-16.770)	<0.001*
APACHE II score	1.167(1.117-1.219)	<0.001*	1.253(1.170-1.343)	<0.001*	1.463(1.333-1.606)	<0.001*	1.576(1.388-1.790)	<0.001*
SIRS score	1.887(1.501-2.372)	<0.001*	1.870(1.476-2.369)	<0.001*	1.970(1.485-2.614)	<0.001*	2.575(1.777-3.729)	<0.001*

Abbreviation: COVID-19, Corona virus disease 2019; CT, Computerized tomography; DIC, Disseminated intravascular coagulation; CD, Cluster of differentiation; NK cells, Natural killer cells; IL-6, Interleukin 6; IL-10, Interleukin 10; IL-8, Interleukin 8; TNF-α, Tumor necrosis factor α; IL-2R, Interleukin 2 receptor; hs-CRP, High-sensitivity C-reactive protein; ALT, Glutamic-pyruvic transaminase; AST, Glutamic-oxaloacetic transaminase; GGT, Gamma-glutamyl transpeptidase; ALB, Albumin; GLO, Globulin; TBIL, Total bilirubin; BUN, Blood urea nitrogen; LDH, Lactic dehydrogenase; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; ALP, Alkaline phosphatase; CK, Creatine kinase; CK-MB, Creatine kinase-MB; hs-cTnI, Hypersensitive cardiac troponin I; TT, Thrombin time; PT, Prothrombin time; APTT, activated partial thromboplastin time; FDP, Fibrinogen degradation products; SOFA, Sequential organ failure assessment; qSOFA, quick SOFA; APACHE II, The acute physiology and chronic health evaluation II; SIRS, The systemic inflammatory response syndrome; ORs and 95% CIs were calculated by univariable and multivariable Logistic regression models. $^{*}P < 0.05$. $^{\beta}$Adjusted for age, sex, comorbidities.

Figures

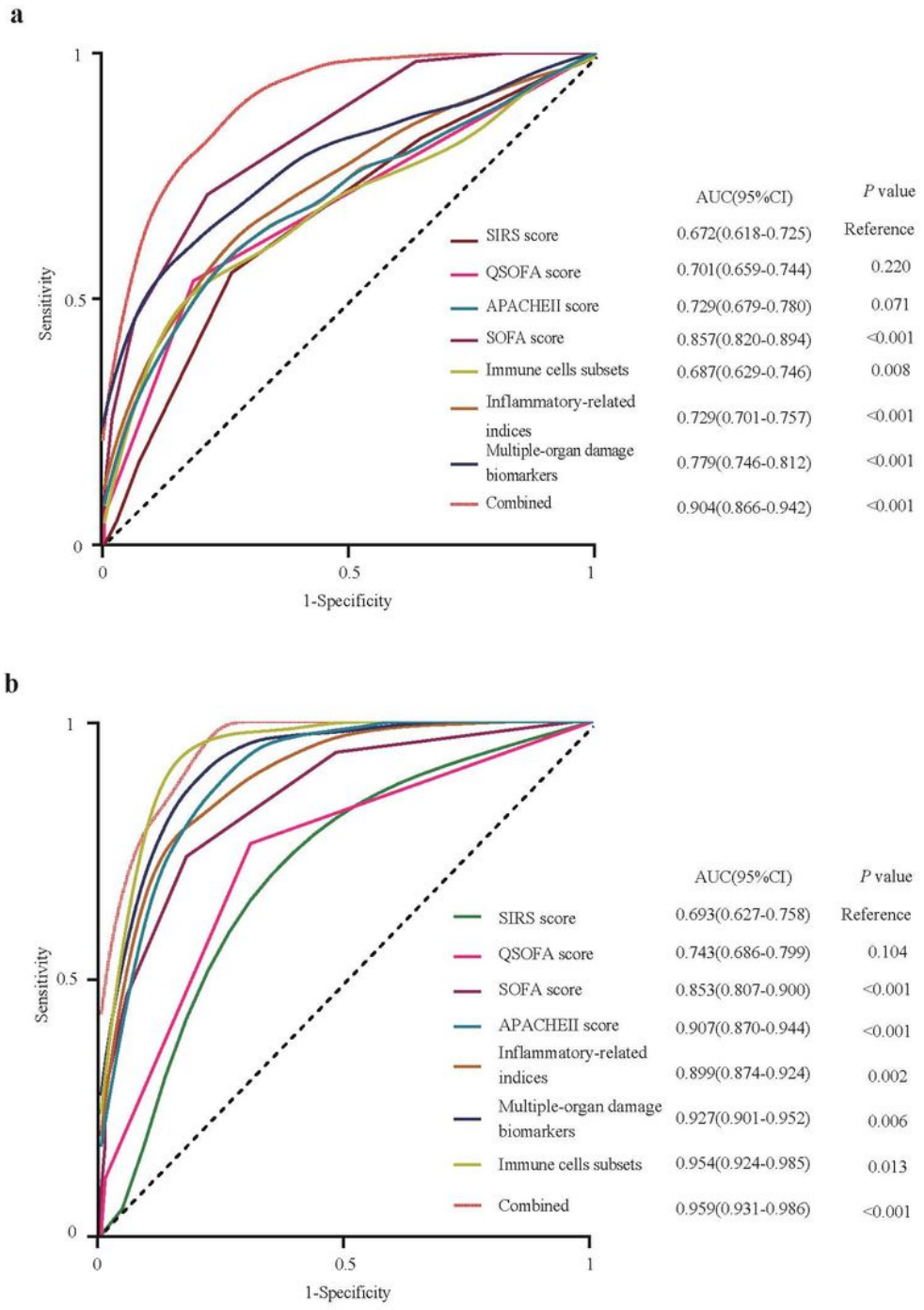

Figure 1

Comprehensive prediction models for ARDS development and progression from ARDS to death in patients with COVID-19 a. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were employed to assess the predictive accuracy of models evaluating the risk of ARDS development for COVID-19 patients with SOFA, qSOFA, APACHE II and SIRS scores, inflammatory-related indexes, immune cell subsets, organ damage indexes, and combined group integrating above mentioned these factors. The

multivariate logistic regression model analysis was used to establish a risk model. The stepwise regression was used for the prediction selection for the model. ROC curves and AUCs (95%CIs) values were generated to assess prognostic accuracy for each model. A two-sided P value < 0.05 was considered statistically significant. b. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were employed to assess the predictive accuracy of models evaluating the death risk of ARDS patients with SOFA, qSOFA, APACHE II and SIRS scores, inflammatory-related indexes, immune cell subsets, organ damage indexes, and combined group integrating above mentioned these factors. The multivariate logistic regression model analysis was used to establish a risk model. The stepwise regression was used for the prediction selection for the model. ROC curves and AUCs (95%CIs) values were generated to assess prognostic accuracy for each model. A two-sided P value < 0.05 was considered statistically significant.

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