Prognostic factors for COVID-19 pneumonia with severe acute respiratory distress syndrome: An observational study.

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Abstract

Objective: To identify the prognostic factors of the coronavirus disease 2019 (Covid-19) pneumonia patients with severe acute respiratory distress syndrome (ARDS).

Design and methods: 45 Covid-19 pneumonia patients with ARDS were included, who were hospitalized at The First Affiliated Hospital of Yangtze University in Jingzhou, Hubei, China, between January 22, 2020, and March 6, 2020. Clinical data and outcomes were reviewed and analyzed according to the Berlin definition.

Results: Males were more likely to develop severe ARDS (11 [91.7%] in males vs. 1 [8.3%] in females). Several factors related to the development of Severe ARDS had been found in this study, which included sex (male) (HR, 13.75; 95% CI, 1.45-130.24), Neutrophil Count (HR, 55.00; 95% CI, 5.02-602.15), Lymphocyte Counts (HR, 40.00; 95% CI, 4.83-331.00), Pro-Thrombin Time (HR, 12.14; 95% CI, 1.19-123.62), D-Dimer (HR, 11.00; 95% CI, 1.16-103.94), Total Bilirubin (HR, 5.00; 95% CI, 0.93-26.79), Albumin (HR, 17.5; 95% CI, 2.67-114.85), Blood Urea Nitrogen (HR, 28.60; 95% CI, 2.89-283.06), Lactate Dehydrogenase (HR, 6.00; 95% CI, 1.17-30.73), C-Reactive Protein (HR, 15.87; 95% CI, 2.40-111.11).

Conclusion: Laboratory tests such as neutrophil count and lymphocyte Counts could play an important role in the diagnosis of severe ARDS and guide treatment decision-making for ARDS patients.

Keywords: Acute respiratory distress syndrome, The coronavirus disease 2019, Pneumonia, Prognostic factors.

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Highlights

We found that Males were more likely to develop severe ARDS.

Several factors related to the development of Severe ARDS had been found in this study, which included neutrophil count and lymphocyte Counts.

Dyspnea andincreased sequential organ failure assessment scoreswere significantly more frequent in patients with severe ARDS.

Patients withsevere ARDS were more likely to receive invasive-mechanical ventilation and develop cardiac injury and shock.

Introduction

The coronavirus disease 2019 (Covid-19) is a recently emerged infectious disease caused by a novel coronavirus (2019-nCoV). The disease has spread rapidly throughout Wuhan (Hubei province) to the world [1-3]. Several studies reported that patients with severe Covid-19 are more likely to develop acute respiratory distress syndrome (ARDS), and have higher mortality [4-6]. For example, among 52 critically ill adult Covid-19 patients in Wuhan Jin Yin-tan hospital (Wuhan, China), 35 patients (67%) developed ARDS, 26 of whom (81%) died [4]. Similarly, among 36 Covid-19 patients hospitalized in the intensive care unit (ICU) of Zhongnan Hospital of Wuhan University, 22 (61.1%) developed ARDS, 6 of whom (27.2%) eventually died [5].ARDS results from direct (e.g., pneumonia or aspiration) or indirect (e.g., extra pulmonary sepsis) lung injury, and has a high mortality rate [7].

Clinically, patients with ARDS develop severe hypoxemia and/or hypercapnia, and most die of sepsis or multiorgan failure rather than from refractory respiratory failure. Hospital mortality of 40% has been reported in patients with ARDS [7,8]. The Berlin definition divides ARDS into three severity of levels based on degree of hypoxemia: mild, moderate, and severe ARDS, and severe ARDS has the highest mortality rate. However, prognostic factors for COVID-19 pneumonia with severe ARDS are still uncertain. In this study, we evaluated ARDS patients with confirmed Covid-19 who were admitted to The First Affiliated Hospital of Yangtze University in Jingzhou, Hubei, China. The objective of this case series was to identify the prognostic factors of Covid-19 pneumonia patients with severe acute respiratory distress syndrome (ARDS) according to the Berlin definition [9].The baseline ARDS morbidity and mortality reported in this study will be of considerable value for the early identification of individuals who are at risk of developing severe ARDS and who are most likely to benefit from further treatment.

Methods

Design and participants

This single-center, retrospective, observational study was conducted at The First Affiliated Hospital of Yangtze University, located in Jing Zhou, Hubei Province, which is responsible for the treatment of Covid-19 patients assigned by the government. In this study, we retrospectively analyzed data from 45 Covid-19 patients that developed ARDS between January 23 and March 6, 2020, Laboratory confirmation of Covid-19 was performed at The First Affiliated Hospital of Yangtze University according to WHO interim guidelines (WHO, 2020), while ARDS diagnosis was performed according to the Berlin definitions[9].Patients died within 24 h of receiving a diagnosis of ARDS were excluded; no children or adolescents were enrolled in the study. At final, 15 patients with mild ARDS, 18 with moderate ARDS, and 12 with severe ARDS patients were included. All chest CT images were reviewed by experienced radiologists. The severity of the ARDS was determined based on the degree of hypoxemia as mild (200 mmHg<PF ratio≤ 300 mmHg), moderate (100 mmHg<PF ratio≤ 200 mmHg), or severe (PF ratio<100 mmHg). This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Yangtze University (No. K20200102). Verbal consent was obtained from all patients.

Data collection

We reviewed the electronic medical records of all patients with laboratory-confirmed Covid-19. Recorded data included demographic information, medical history, exposure history, comorbidities, symptoms, signs, laboratory findings, treatments, and outcomes. The majority of clinical data regarding Systolic Pressure, Respiratory Rate, Blood Routine Blood Test, Coagulation, Biochemical Tests, Chest CT Scans, as well as Partial Pressure of Arterial Oxygen (PaO2)/fraction of inspired oxygen (FIO2) were obtained within 24 hours of ARDS diagnosis. Shock was defined according to the guidelines of WHO for novel coronavirus disease 2019 (COVID-19), while acute kidney injury was diagnosed based on serum creatinine levels [4,10,11]. Cardiac injury was diagnosed if the serum concentration of hypersensitive cardiac troponin I (hsTNI) was above the upper limit of the reference range (34.2 pg/mL)[4]. All clinical data were reviewed by an experienced team of physicians. Any missing or uncertain records were collected and clarified through direct communication with involved health-care providers and the families of the patients.

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR), and comparisons were performed using the Kruskal-Wallis H test. Categorical variables were expressed as number (%) and compared using the chi-squared test or Fisher's exact test among patients with mild, moderate, and severe ARDS. We used a Kaplan Meier plot for survival data. Mantel-Cox (log-rank) tests were performed to compare survival curves. Multivariate Cox proportional hazard ratio (HR) models were used to determine HRs and 95% CIs between individual factors on the development of ARDS. All statistical tests were two-sided, with the significance threshold set at $\alpha<0.05$. Statistical analyses were conducted using the SPSS software, version 17.0.

Results

Clinical characteristics and symptoms

In this study, we retrospectively analyzed data from 45 Covid-19 patients that developed ARDS between January 23 and March 6, 2020; no children or adolescents were enrolled in the study. All study participants were residents of Jing Zhou City. The median age was 64 years (IQR, 53-73; range, 18-88 years; p>0.929). 22(48.9%) were older than 65 years, 6 of whom had mild ARDS, 9 had moderate ARDS, and 7 had severe ARDS; 29 (64.4%) patients were males, while the remaining 16 (35.6%) were females. 30 (66.7%) patients had a contact history with the epidemic area of Wuhan. Compared with females, male patients were more likely to develop to severe ARDS (11 [91.7%] in males vs 1 [8.3%] in females, p=0.044). The median duration between the first symptoms and ARDS development was 8 days (IQR, 3-16; Table 1). 30 of 45 ARDS patients (66.7%) had at least one Chronic Disease, including Diabetes (n=4; 8.9%), Hypertension (n=17; 37.8%), Cardiovascular Disease (n=4; 8.9%), Chronic Obstructive Pulmonary Disease (n=4; 8.9%), and Cancer (n=1; 2.2%). There was no significant difference in the incidence of chronic illness among patients with different severity ARDS. Patients with ARDS experienced Fever (n=45; 100%), Dry Cough (n=41; 91.1%), Chest Pain (n=40; 88.9%), Dyspnea (n=33; 73.3%), Fatigue (n=22; 48.9%), and Vomiting (n=19; 42.2%). Less frequent symptoms included Diarrhea (n=8; 17.8%), Haemoptysis (n=1; 2.2%), and Dorsalgia (n=6; 13.3%). Dyspnea was significantly more frequent in patients with severe ARDS, compared with patients with mild and moderate

ARDS (mild: 53.3%, moderate: 72.2%, and severe: 100%, p=0.017; Table 1).

		All Patients	Mild	Moderate	Severe
	(n=45)	(n=15)	(n=18)	(n=12)	p values
Age, Median(IQR), Y	64(53-73)	63(54-72)	65(47-75)	66(52-73)	0.929
≤ 65	23(51.1%)	9(60.0%)	9(50.0%)	5(41.7%)	0.644
>65	22(48.9%)	6(40.0%)	9(50.0%)	7(58.3%)	
Sex					
Female	16(35.6%)	8(53.3%)	7(38.9%)	1(8.3%)	0.044
Male	29(64.4%)	7(46.7%)	11(61.1%)	11(91.7%)	
Onset of Symptom to ARDS, Median (IQR), D	8(3,16)	8(2,19)	7(4,16)	7(2,15)	0.944
Contact History of Epidemic Area					
Wuhan	30(66.7%)	8(53.3%)	12(66.7%)	10(83.3%)	0.238
Jingzhou	15(33.3%)	7(46.7%)	6(33.3%)	2(16.7%)	
Chronic Medical Illness	30(66.7%)	9(60.0%)	15(83.4%)	6(50%)	
Diabetes	4(8.9%)	1(6.7%)	2(11.1%)	1(8.3%)	>0.99
Hypertension	17(37.8%)	6(40.0%)	7(38.9%)	4(33.4%)	>0.99
Cardiovascular Disease	4(8.9%)	1(6.7%)	2(11.1%)	1(8.3%)	>0.99
Chronic Obstructive					
Pulmonary Disease	4(8.9%)	1(6.7%)	3(16.7%)	0(0%)	0.434
Malignancy	1(2.2%)	0(0%）	1(5.6%)	0(0%)	>0.99
Current Smoking	4(8.9%)	1(6.7%)	1(5.6%)	2(16.7%)	0.656
Signs and Symptoms					
Fever	45(100%)	15(100%)	18(100%)	12(100%)	>0.99
Dry Cough	41(91.1%)	14(93.3%)	16(88.9%)	11(91.7%)	>0.99
Dyspnea	33(73.3%)	8(53.3%)	13(72.2%)	12(100%)	0.017
Vomiting	19(42.2%)	6(40%)	8(44.4%)	6(50%)	0.931
Fatigue	22(48.9%)	9(60%)	8(44.%)	5(41.7%)	0.6
Chest Pain	40(88.9%)	12(80%)	16(88.9%)	12(100%)	0.35
Haemoptysis	1(2.2%)	0(0%)	0(0%)	1(8.3%)	0.272
Dorsalgia	6(13.3%)	3(20.0%)	1(5.6%)	2(16.7%)	0.477
Diarrhea	8(17.8%)	4(26.7%)	3(16.7%)	1(8.3%)	0.486

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. p values comparing among Mild, Moderate and Severe groups are from χ^2 test, Fisher's exact test, or Kruskal-Wallis H test.

Table 1.*Characteristics and symptoms of Covid-19 patients who developed ARDS.*

Comorbidities and prognosis

The median systolic pressure, respiratory rate, pH, PO_2, PCO_2, PO_2/FiO_2 were 123 mmHg (IQR, 112-152), 30.5 (IQR, 30-35), 7.45 (IQR, 7.42-7.48), 68 mmHg (IQR, 55.5-75), 35.6 mmHg (31.8-41.1), and 150 mmHg (IQR, 92.7-218), respectively (Table 2). Compared with patients with mild and moderate ARDS, the median respiratory rate and pH were higher in patients with severe ARDS (p=0.018 for respiratory rate and p=0.001 for pH). Additionally, the median PO_2 and PO_2/FiO_2 were significantly lower in patients with severe ARDS ($p<0.001$ for PO_2, and $p<0.001$ for PO_2/FiO_2, respectively) compared with patients with mild ARDS. The median systolic pressure and PCO_2 did not differ significantly among the three patient groups. On th e day of ARDS diagnosis, the median

Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE II), and Sequential Organ Failure Assessment scores (SOFA) were 14 (IQR, 9-15), 16 (IQR, 12-24), and 4 (IQR, 3-6), respectively. Compared with the other two ARDS groups, the median GCS, APACHE II, and SOFA were significantly higher in the severe ARDS group ($p=0.025$ for GCS; $p<0.001$ for APACHE II; $p<0.001$ for SOFA). The Sequential Organ Failure Assessment scores (SOFA) of five severe ARDS patients that died were higher than five.

	All Patients	**Mild**	**Moderate**	**Severe**	
	(n=45)	(n=15)	(n=18)	(n=12)	p values
Systolic Pressure, Median (IQR),Mm Hg	123(112-152)	116(112-137)	124(113-147)	115(88-125)	0.47
Respiratory Rate, Median (IQR)	30.5(30-35)	30(29-31)	34.5(30.3-36.5)	33(29.3-39)	0.04
PH, Median(IQR)	7.45(7.42-7.48)	7.42(7.4-7.43)	7.47(7.45-7.49)	7.47(7.42-7.48)	0
PO_2, Median(IQR)	68(55.5-75)	75(72-80)	66.4(59.5-74.3)	53.2(45.6-56.8)	<0.001
PCO_2, Median(IQR)	35.6(31.8-41.1)	40.2(32.8-41.4)	34.3(31.6-37.2)	35.5(30.4-41.2)	0.36
PO_2/Fio_2, Median(IQR)	150(92.7-218)	228(219.5-245)	138.5(106.3-168.4)	78.3(72.5-86.8)	<0.001
Acute Physiology and Chronic Health Evaluation II	16(12-24)	12(10-16)	16(12-20)	28(23-37)	<0.001
Glasgow Coma Scale Score	14(9-15)	15(14-15)	12.5(11.25-15)	8(7-15)	0.03
Sequential Organ Failure Assessment Scores	4(3-6)	3(2.5-4)	4(3-5)	7(5.75, 9.25)	<0.001
Comorbidities					
Acute Kidney Injury	7(15.6%)	2(13.3%)	2(11.1%)	3(25%)	0.59
Cardiac Injury	9(20%)	1(6.7%)	2(11.1%)	6(50.0%)	0.01
Liver Dysfunction	20(44.4%)	4(26.7%)	11(61.1%)	5(41.7%)	0.14
Hyperglycaemia	12(26.7%)	1(6.7%)	6(33.3%)	5(41.7%)	0.07
Pneumothorax	2(4.4%)	0(0%)	0(0%	2(16.7%)	0.07
Shock	5(11.1%)	0(0%	1(5.6%)	4(33.4%)	0.03
Treatment					
High Flow Nasal Cannula	24(53.3%)	8(53.3%)	10(55.6%)	6(50.0%)	>0.99
Mechanical Ventilation	45(100%)	15(100%)	18(100%)	12(100%)	>0.99
Non-Invasive	40(88.9%)	15(100%)	16(88.9%)	9(75.0%)	0.13
Invasive	9(20%)	0(0%)	3(16.7%)	6(50%)	0.01
Prone Position Ventilation	15(33.3%)	1(6.7%)	6(33.3%)	9(75.0%)	0
Antiviral Agents	45(100%)	15(100%)	18(100%)	12(100%)	>0.99
Antibacterial Agents	6(13.3%)	0(0%)	1(5.6%)	5(41.7%)	0
Glucocorticoids	38(84.4%)	12(80.0%)	15(83.3%)	11(91.7%)	0.77
Inhibitor	4(8.9%)	2(13.3%)	2(11.1%)	0(0%	0.55
Interferon	8(17.8%)	0(0%	3(16.7%)	5(41.7%)	0.02
Immunoglobulin	32(71.1%)	7(46.7%)	15(83.3%)	10(83.3%)	0.06
Prognosis					
Hospitalisation	22(48.9%)	5(33.3%)	11(61.1%)	6(50%)	0.29
Discharge	16(35.6%)	9(60.0%)	6(33.3%)	1(8.3%)	0.02
Death	7(15.6%)	1(6.7%)	1(5.6%)	5(41.7%)	0.02

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. p values comparing among Mild,Moderate and Severe groups are from χ^2 test, Fisher's exact test, or Kruskal-Wallis H test.

Table 2.*Comorbidities and prognosis of Covid-19 patients who developed ARDS.*

Most Covid-19 patients with ARDS exhibited organ function failure, including Liver Dysfunction (n=20; 44.4%), Hyperglycemia (n=12; 26.7%), Cardiac Injury (n=9; 20%), Acute Kidney Injury (n=7; 15.6%), Shock (n=5; 11.1%), and Pneumothorax (n=2; 4.4%; Table 2). Compared with patients with mild and moderate ARDS, cardiac injury and shock were significantly more frequent in patients with severe ARDS(p=0.013 for cardiac injury and p=0.026 for shock, respectively.

Among the 45 ARDS patients, 24 (53.3%) were treated with high flow nasal cannula. 45 (100%) received mechanical ventilation, including 40 (88.9%) patients that were on non-invasive ventilation and 9 (20%) patients that received invasive mechanical ventilation; 15 (33.3%) patients required prone position ventilation. Additionally, 45 (100%) patients were treated with antiviral agents (Arbidol). 38 (84.4%)
patients received glucocorticoids (Methylprednisolone), and 32 (71.1%) received immunoglobulin. Interferon (Thymalfasin), the Anti-Bacterial Agent Lopinavir, and Chloroquine were administered to 8 (17.8%), 6 (13.3%), and 4 (8.9%) patients, respectively (Table 2).

Compared with patients with mild ARDS and moderate ARDS, patients with severe ARDS were more likely to require invasive mechanical ventilation (p=0.005), prone position ventilation (p=0.001), antibacterial agents (p=0.004), and interferon (p=0.017). Although antiviral agents (n=12; 100%) and glucocorticoids (n=11; 91.7%) were widely used in patients with severe ARDS, there was no significant difference in the frequency of the use of these agents among the different groups (Table 2).

Survival curves for different severity of ARDS patients

Among the 45 patients with ARDS, 22 patients remained hospitalized (48.9%), 16 were discharged (35.6%), and 7 (15.6%) died. Compared with patients with mild and moderate ARDS, patients with severe ARDS had a higher mortality rate (mild: 6.7%, moderate: 5.6%, severe: 41.7%, p=0.018; Table 2).

In this cohort, among discharged patients (n=16), the median hospital stay was 29 days (IQR, 19.0-38.0). Among patients that died of ARDS (n=7), the median duration from admission to death was 14 (IQR, 7-17) days. Kaplan Meier survival curves for different severity of ARDS patients showed significant difference between three groups (log-rank tests, p=0.034) (Figure 1).

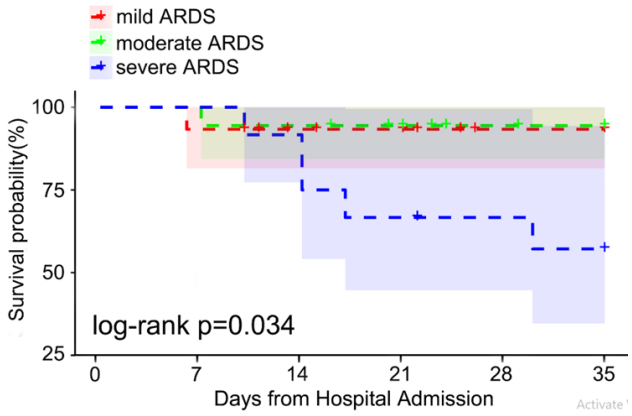

Figure 1.*Survival of Covid-19 patients who developed ARDS. Red, green, and blue regions represent 95% CIs for mild ARDS, moderate ARDS, and severe ARDS patients, respectively.*

Laboratory findings

Compared with patients with mild and moderate ARDS, a higher portion of patients with severe ARDS had low lymphocyte count (mild: 1.1 × 109/L, IQR, 0.71-1.34; moderate: 0.73 × 109/L, IQR, 0.6-0.9; severe: 0.26 × 109/L, IQR, 0.21-0.36; p<0.001), low albumin levels (mild: 37.4 g/L, IQR, 37.75-40.7; moderate: 36.6 g/L, IQR, 35.1-39.5; severe: 34g/L, IQR, 31.9-34.4; p=0.004), high white blood cell count (mild: 5.78 × 109/L, IQR, 3.9-7.2; moderate: 8.2 × 109/L, IQR, 4.8-11.7; severe: 8.99 × 109/L, IQR, 7.25-13.22; p=0.009), high neutrophil count (mild: 4.48 × 109/L, IQR, 2.47-5.26; moderate: 7.02 × 109/L, IQR, 3.57-10.2; severe: 8.24 × 109/L, IQR, 6.73-12.6; p=0.001), prolonged prothrombin time (mild: 11.1 s, IQR, 10.75-11.7; moderate: 10.5 s, IQR, 9.77-11.67; severe: 11.8s, IQR, 11.45-12.8; p=0.035), increased D-dimer (mild: 0.46 mg/L, IQR, 0.34-1.15; moderate: 1.15 mg/L, IQR, 0.63-2.18; severe: 7mg/L, IQR, 4.4-17.1; p<0.001), high total bilirubin levels (mild: 10.7 mmol/L, IQR, 7.7-13.7; moderate: 13.5 mmol/L, IQR, 11.3-17.8; severe: 19.2 mmol/L, IQR, 14.1-23.6; p=0.021), high lactate dehydrogenase levels (mild: 213 U/L, IQR, 185-260; moderate: 260.5 U/L, IQR, 228.7-315.5; severe: 356 U/L, IQR, 256.5-466.7; p=0.009), high blood urea nitrogen levels (mild: 5.04 mmol/L, IQR, 3.42-5.9; moderate: 6.98 mmol/L, IQR, 5.37-9.57; severe: 9.4 mmol/L, IQR, 7.5-11.9; p=0.003), and high C-reactive protein levels (mild: 7.02 mg/L, IQR, 2.27-14.9; moderate: 13.19 mg/L, IQR, 4.39-16.44; severe: 60 mg/L, IQR, 14.5-121; p=0.013;) (Table 3).

		All patients	**Mild**	**Moderate**	**Severe**	
	Normal range	(n=45)	(n=15)	(n=18)	(n=12)	p values
White blood cell count, × 10^9 per L	3.5-9.5	7.1(5.5-10.9)	5.78(3.9-7.2)	8.2(4.8-11.7)	8.99(7.25-13.22)	0.009
Neutrophil count, × 10^9 per L	1.8-6.3	6.3(4.08-10.1)	4.48(2.47-5.26)	7.02(3.57-10.2)	8.24(6.73-12.6)	0.001

Lymphocyte count, × 10^9 per L	1.1-3.2	0.69(0.42-1.1)	1.1(0.71-1.34)	0.73(0.6-0.9)	0.26(0.21-0.36)	<0.001
Lymphocyte percentage, %	20-50	9.7(3.84-17.9)	18.5(12.3-29.35)	9.16(7.55-15.65)	2.95(2.475-3.93)	<0.001
Red blood cell count, × 10^9 per L	3.8-5.1	3.81(3.32-4.02)	3.75(3,16-4.02)	3.7(3.27-4.07)	3.91(3.61-4.12)	0.564
Haemoglobin, g/L	115-150	118(99-127)	112.5(96.9-125.8)	116(105-129)	102(87.7-120)	0.224
Platelet count, × 10^9 per L	125-350	155(114-197)	143(122-182.5)	149.5(101.2-194.5)	177.5(140-215.7)	0.62
Prothrombin time, s	9.9-12.5	11.3(10.5-11.9)	11.1(10.75-11.7)	10.5(9.77-11.67)	11.8(11.45-12.8)	0.035
Activated partial thromboplastin time, s	23-38	27.2(22.6-32.4)	27.2(22.7-30.15)	27.15(22.02-33.52)	30.8(24.75-34.1)	0.704
D-dimer, mg/L	≤ 0.50	1.16(0.51-3.28)	0.46(0.34-1.15)	1.15(0.63-2.18)	7(4.4-17.1)	<0.001
Fibrinogen, g/L	1.8-3.5	3.53(2.76-4.65)	3.69(3.2-4.1)	3.65(2.64-4.61)	3.13(2.58-6.47)	0.981
Total bilirubin, mmol/L	2-20.4	13(10.1-21.8)	10.7(7.7-13.7)	13.5(11.3-17.8)	19.2(14.1-23.6)	0.021
Albumin, g/L	35-55	35.8(34.1-38.2)	37.4(37.75-40.7)	36.6(35.1-39.5)	34(31.9-34.4)	0.004
Alanine aminotransferase, U/L	Jan-40	35(18-64)	32(18-42.5)	53(29.25-89.5)	32(25.7-65.7)	0.296
Aspartate aminotransferase, U/L	Feb-42	31(24-49)	27(24.5-36.5)	41(26.25-56.75)	33(24.75-34.1)	0.155
Potassiun ion, mmol/L	3.5-5.5	4.3(3.9-4.7)	4.3(3.95-4.65)	4.2(3.9-4.75)	4.35(3.9-4.7)	0.916
Creatine Kinase, U/L	26-140	47(27.5-134.5)	37(29.5-100.75)	63(21-148)	46(33.75-99.0)	0.962
Creatine Kinase-MB, U/L	≤ 20	16(10.5-20.5)	11.5(9-18.75)	15(12-20)	19(15.5-27)	0.09
Glutamy transpeptidase, U/L	≤ 50	52(24-87)	43(22-53)	52(24-92.25)	65(43.75-157.5)	0.087
Blood urea nitrogen, mmol/L	1.8-7.00	7.06(5.04-9.8)	5.04(3.42-5.9)	6.98(5.37-9.57)	9.4(7.5-11.9)	0.003
Creatinine, μmol/L	44-106	65.4(58.9-79.7)	75.8(57.4-85.7)	62.45(58.25-73.7)	63.9(61.3-79.7)	0.746
Lactate dehydrogenase, U/L	100-240	252(208-331)	213(185-260)	260.5(228.7-315.5)	356(265.5-466.7)	0.009
High sensitibe troponin, pg/mL	≤ 34.2	8(4.5-13.5)	4.9(2.15-10.7)	8.25(4.65-12.52)	14.7(5.17-34.97)	0.134
Brain natriuretic peptide, pg/mL	≤ 100	52.7(19.5-226.8)	62.3(20.95-194.7)	30.25(16.05-137.5)	122.5(34.15-466.95)	0.21
C-reactive protein, mg/L	≤ 8	13.6(3.97-42.01)	7.02(2.27-14.9)	13.19(4.39-16.44)	60(14.5-121)	0.013
Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. p values comparing among Mild, Moderate and Severe groups are from χ^2 test, Fisher's exact test, or Kruskal-Wallis H test.						

Table 3.*Laboratory findings in Covid-19 patients who developed ARDS.*

Multivariate COX regression analysis of prognostic factors

Multivariate Cox models showed that several factors related to the development of Severe ARDS, which included sex (male) (HR, 13.75; 95% CI, 1.45-130.24), Neutrophil count (HR, 55.00; 95% CI, 5.02-602.15), Lymphocyte Counts (HR, 40.00; 95% CI, 4.83-331.00), Prothrombin time (HR, 12.14; 95% CI, 1.19-123.62), D-dimer (HR, 11.00; 95% CI, 1.16-103.94), Total bilirubin (HR, 5.00; 95% CI, 0.93-26.79), Albumin (HR, 17.5; 95% CI, 2.67-114.85), Blood urea nitrogen (HR, 28.60; 95% CI, 2.89-283.06), Lactate dehydrogenase (HR, 6.00; 95% CI, 1.17-30.73), C-reactive protein (HR, 15.87; 95% CI, 2.40-111.11) (Table 4).

	Mild ARDS		**Severe ARDS**	
	HR (95%CI)	**p values**	**HR (95%CI)**	**p values**
Sex (Female, male)	2.50(0.60-10.34)	0.206	13.75(1.45-130.24)	0.022
Age (≤ 65, >65), y	0.67(0.17-2.67)	0.566	1.4(0.32-6.11)	0.654
Diabetes	2.62(0.21-32.08)	0.452	1.55(0.09-27.36)	0.767
Hypertension	1.05(0.26-4.26)	0.948	0.79(0.17-3.63)	0.757
White blood cell count	5.33(0.89-32.16)	0.068	5.71(0.89-36.89)	0.067

Neutrophil count	5.71(1.15-28.35)	0.033	55.00(5.02-602.15)	0.001
Lymphocyte count	0.57(0.05-7.00)	0.662	40.00(4.83-331.00)	0.001
Red blood cell count	1.43(0.36-5.66)	0.611	1.75(0.40-7.66)	0.458
Haemoglobin	0.39(0.08-1.91)	0.247	0.52(0.10-2.63)	0.432
Platelet count	0.88(0.16-4.71)	0.876	0.70(0.11-4.59)	0.71
Prothrombin time, s	2.62(0.21-32.08)	0.452	12.14(1.19-123.62)	0.035
D-dimer	2.75(0.63-11.97)	0.178	11.00(1.16-103.94)	0.036
Fibrinogen	0.73(0.18-2.91)	0.653	0.46(0.10-2.01)	0.299
Total bilirubin	1.25(0.21-7.35)	0.805	5.00(0.93-26.79)	0.06
Albumin	1.27(0.26-6.27)	0.767	17.5(2.67-114.85)	0.003
Alanine aminotransferase	2.36(0.58-9.58)	0.231	1.12(0.25-4.97)	0.879
Aspartate aminotransferase	4.38(0.88-21.71)	0.071	3.57(0.66-19.34)	0.14
Creatine Kinase	1.82(0.34-9.83)	0.487	1.67(0.28-10.09)	0.578
Creatine Kinase-MB	1.25(0.21-7.35)	0.805	3.57(0.66-19.34)	0.14
Glutamy transpeptidase	1.79(0.45-7.20)	0.408	3.14(0.68-14.50)	0.142
Blood urea nitrogen	2.28(0.54-9.67)	0.265	28.60(2.89-283.06)	0.004
Creatinine	2.00(0.29-13.91)	0.484	2.67(0.37-19.06)	0.328
Lactate dehydrogenase	4.00(0.94-17.11)	0.062	6.00(1.17-30.73)	0.032
High sensitibe troponin	NA	NA	5.67(0.51-62.66)	0.157
C-reactive protein	2.94(0.45-20.00)	0.261	15.87(2.40-111.11)	0.004

Table 4.*Multivariate Cox Regression of Factors Associated With ARDS Development in Covid-19 patients*.

Discussion

It has become evident that Covid-19 patients are at risk of developing ARDS[4-6]. Severe ARDS has the highest mortality rate among three severity levels of ARDS [9]. However, Prognostic factors for COVID-19 pneumonia with severe acute respiratory distress syndrome are still uncertain. In this single-centered, retrospective, observational study, we stratified patients into three groups (mild, moderate, and severe ARDS) according to Berlin severity definitions. We assessed differences in clinical characteristics and outcomes among the different patient groups and found that male patients were more likely to develop severe ARDS. We also found that patients with severe ARDS were more likely to experience severe respiratory failure, sepsis, cardiac injury, and shock. Laboratory findings, including high neutrophil counts, low lymphocyte count, low albumin levels, prolonged prothrombin time, as well as high D-dimer, lactate dehydrogenase, blood urea nitrogen, and C-reactive protein levels. Laboratory tests such as neutrophil count and lymphocyte Counts could play an important role in the diagnosis of severe ARDS and guide treatment decision-making for ARDS patients.

Several studies reported that nearly 70% of patients confirmed with Covid-19 were men [1,2]. Moreover, elderly patients have a higher Covid-19-associated mortality rate compared with younger individuals [4]. These findings suggest that older, male patients are the most susceptible to Covid-19 infection [2]. Consistently, we found that of the 45 enrolled ARDS patients, a high proportion included elderly or male patients. Furthermore, we found that males were more likely to develop severe ARDS compared to females (p=0.044). However, the mechanism underlying this phenomenon remains unclear.

Wu et al. found that several factors that were associated with the development of ARDS, including fever, comorbidities, AST, creatinine, and glucose levels, were not associated with mortality [12,13]. In this study, we could not find an association between ARDS severity and disease Signs and Symptoms, Including Fever, Dry Cough, Vomiting, Fatigue, Chest Pain, Hemoptysis, Dorsalgia, and Diarrhea). The presence of chronic diseases, including diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and cancer, were also not linked to the risk of severe ARDS development. Additionally, we found no association between ARDS severity and organ dysfunction, including acute kidney injury, liver dysfunction, and hyperglycemia.

In this study, we found that the incidence of severe ARDS was higher in patients with low lymphocyte count, high white blood cell count, and high neutrophil count. Neutrophilia has been observed both in the peripheral blood and lungs of patients with Covid-19, and neutrophils were identified as the primary

source of chemokines and cytokines [14-16]. Patients with severe ARDS had a significantly higher neutrophil count compared with patients with mild or moderate ARDS. Elevated neutrophil numbers were likely due to host immune responses against the virus, contributing to cytokine storm. Lymphopenia has also been reported in patients with Covid-19 and has been suggested as a critical factor associated with disease severity [2,5,16,17]. Consistent with previous reports that lymphopenia could increase inflammation, we found that compared to patients with mild or moderate ARDS, patients with severe ARDS had higher levels of C-reactive protein, a marker of generalized inflammation [18].

Low albumin levels, prolonged prothrombin time, and high D-dimer, lactate dehydrogenase, total bilirubin, and blood urea nitrogen levels were associated with high mortality in ARDS patients [4,12]. The predictive value of albumin and lactate dehydrogenase levels may be higher in monitoring the severity and course of ARDS in critically ill patients [19]. Previous studies demonstrated that prolonged prothrombin time and high D-dimer were associated with excessive thrombin generation, inhibition of fibrinolysis, endothelial damage, and capillary leakage, which could increase the severity of ARDS [20]. Consistent with these results, we found that low albumin and prolonged prothrombin time, as well as high D-dimer, total bilirubin, lactate dehydrogenase, and blood urea nitrogen were all factors significantly associated with risk of severe ARDS development. These results suggest that laboratory findings could provide a powerful tool guiding severe ARDS diagnosis.

In this study, we found that ARDS development was associated with the presence of various dysfunctions and complications, such as severe respiratory failure, hypoxemia, sepsis, multiple systemic organ failure, and shock. We also found that the respiratory rate and pH were significantly higher in patients with severe ARDS, while the median PO_2 and PO_2/FiO_2 were lower. The incidence of dyspnea was significantly higher in patients with severe ARDS, who required mechanical ventilation more frequently. Additionally, cardiac injury and shock were more prevalent among patients with severe ARDS. As patients with ARDS often develop severe hypoxemia and hypercapnia and most die of sepsis or multiorgan failure rather than refractory respiratory failure, future studies are needed to explore the prognostic value of SOFA scores in Covid-19 patients [7,8].

This study has several limitations. Importantly, this was a single-center study with a limited sample size. Potential selection bias may have been introduced when identifying factors that influence clinical outcomes, and large multi-center studies are required to further define the clinical characteristics and risk factors of ARDS development in Covid-19 patients. Furthermore, this was a retrospective study; hence, the data of this study permit a preliminary assessment of the clinical course and outcomes of ARDS patients with Covid-19, and further studies are required to confirm our findings.

Conclusion

In conclusion, the mortality Covid-19 patients with severe ARDS are considerably higher compared with patients with mild ARDS symptoms. Male patients with low lymphocyte count, high neutrophil count, prolonged prothrombin time, low albumin, as well as high D-dimer, lactate dehydrogenase, total bilirubin, blood urea nitrogen, and C-reactive protein levels have a higher risk of developing severe ARDS. Laboratory tests could play an important role in the diagnosis of severe ARDS and guide treatment decision-making for ARDS patients.

Conflict of Interest

There is no conflict of interest.

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Cunjian Yi, Jinzhi Lu and Ying Xiong conceived and designed the study. They had full access to all data and were responsible for data analysis integrity and accuracy. Cunjian Yi, Jinzhi Lu and Ying Xiong wrote the manuscript. Liya Zhu, Ying Xiong, Xiangqiong Liu, Zhiqiang Liu, and Cunjian Yi revised the manuscript. Zhiqiang Liu, ChenqiXin, and Yujiechen performed the statistical analyses. All authors contributed to data acquisition, data analysis, or data interpretation, as well as reviewed and approved the final version of the manuscript.

Data Sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request. Participant data without names and identifiers will be made available after approval from the corresponding author and the National Health Commission. After publication of study findings, the data will be available for others upon request. An email address will be provided for correspondence once data sharing is approved. A proposal with a detailed description of study objectives and statistical analysis will be required for the evaluation of data sharing requests by the corresponding author and the National Health Commission. Additional materials may also be required during the process.

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