Difference in Risk Factors Associated with Acute Respiratory Distress Syndrome and Intubation/Death in Patients with Coronavirus Disease 2019: A Two-hospital Retrospective Cohort Study in Hubei, China

Jing-Lan Mu (✉ mujinglanbb@gmail.com)

Drum Tower Hospital, Medical Department of Nanjing University

Ming-Zhe Qin

General Hospital of Central Theatre Command of PLA

Hui-Mei Sun

Nanfang Hospital, Southern Medical University

Bao-Sheng Guo

Drum Tower Hospital, Medical Department of Nanjing University

Shi-Da Qiu

Nanfang Hospital, Southern Medical University

Fu Zhang

Nanfang Hospital, Southern Medical University

Huang Yang

Nanfang Hospital, Southern Medical University

Juan Nie

The People's Hospital of Honghu

Xu-Dong Liu

Sun Yat-sen University

Wing-Fai Yeung

The Hong Kong Polytechnic University, Hong Kong

Xiao-Dong Liu

The Chinese University of Hong Kong, Hong Kong

Ye-Hong Dong

Nanfang Hospital, Southern Medical University

Bi-Xi Li

General Hospital of Central Theatre Command of PLA

Xiao-Yang Song

General Hospital of Central Theatre Command of PLA

Shao-Yan Lin

Nanfang Hospital, Southern Medical University

Ke-Xuan Liu

Nanfang Hospital, Southern Medical University

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Abstract

Background: The reviews on the risk factors with ARDS and the worse outcomes concluded lacking robust data of risk factors to prevent COVID-19 and identified an urgent need for large sample and high-quality research in this area, as well as the features of the ARDS.

Methods: This retrospective cohort study included 333 COVID-19 inpatients at two hospitals in Hubei of China in 2020. The COVID-19-related ARDS was diagnosed according to the Berlin criteria. The outcomes were ARDS development and the intubation or in-hospital death. The cox proportional hazard ratio (HR) models were employed to determine the significant risk factors.

Results: The median number of days from symptom onset to ARDS diagnosis was 11.0 (IQR, 8.0–13.0). Up to 84.1% COVID-19-related ARDS patients demonstrated multiple organ injuries. The mortality rates were 41.9% and 85.7% in moderate and severe ARDS. The survival patients on invasive mechanical ventilation (IMV) had been intubated earlier since ARDS diagnosis than those who had not survived (5.5 median days, IQR 4.0-7.0 days versus 11.5 median days, IQR 6.0-14.0 days, $P < 0.001$). Males and all abnormal laboratory indices associated with the higher risk of ARDS ($P < 0.05$) but were not linked with the risk of intubation or death ($P > 0.05$). The sensitivity analyses found that lymphocyte count of < 1000 per mm^3 at hospital admission were still significantly associated with developing ARDS when adjusting for age and male gender (HR, 4.10; 95% CI, 2.40-7.10), and oxygenation index (OI) ratio < 150 were more likely to predict the intubation/death after age adjustment (HR, 2.50; 95% CI, 1.17-5.30).

Conclusion: The SARS-CoV-2-caused ARDS was not the typical ARDS according to Berlin criteria. The alive patients with IMV had been intubated earlier since ARDS diagnosis than those who had not survived. We identified male gender and abnormal laboratory indices associated with the ARDS but were not linked with the intubation/death. Sensitivity analysis concluded lymphocyte count of < 1000 per mm^3 could predict ARDS while OI ratio less than 150 could predict intubation/death.

Introduction

Since the COVID-19 outbreak in December 2019 in Wuhan of China, it has rapidly developed into a worldwide pandemic, with more than 129 million patients infected which resulted in over 2 million deaths until March 2021 (1). The data published suggest that 5–20% of COVID-19 patients develop severe illness that is characterized by acute respiratory distress syndrome (ARDS), the mainstay of treatment for which is mechanical ventilation (2–4). However, the mortality has been reported ranging from 30–80% in the COVID-19 patients who progressed into invasive mechanical ventilation (IMV) (2, 4).

The systematic review on risk factors with ARDS reported lacking robust data of risk factors to prevent COVID-19 and identified an urgent need for high quality research in this area (5). The previous studies generally suffered from unclear definition, small sample sizes, and a lack of adjustment for confounders (5). Until now, the risk factors leading to the intubation or death have not been well delineated (4, 6). As those patients with ARDS who progressed on intubation and mechanical ventilation had higher deaths (2, 4), identifying the relevant risk factor associated with the intubation or death in the population could change the worst outcomes waiting for global populations fully vaccinated. Additionally, the views that COVID-19 causing an “atypical” ARDS remain different

and have been discussed (7, 8). Comparably large studies are really required to conclude that if COVID-19-related ARDS has different features.

To make full use of the past valuable medical records and improve the future clinical outcomes for the pandemic particularly in several countries, we retrospectively compared the clinical features between COVID-19 patients with ARDS and those without ARDS, and between subgroups of intubation and never intubation in COVID-19 patients from two hospitals of Hubei of China. We analysed the initial intubation time between survivors and non-survivors who were given IMV. We then studied the risk factors for COVID-19 ARDS and the ARDS patients who progressed into intubation or death.

Methods

Study design and participants

This retrospective cohort study included adult COVID-19 inpatients (≥ 18 years old) from 26 January 2020 to 1 April 2020 treated at General Hospital of Central Theatre Command of PLA in Wuhan (a tertiary hospital) and at People's Hospital of Honghu (a community hospital) in Jingzhou, a city close to Wuhan, in Hubei province, China. COVID-19 was diagnosed based on the World Health Organization (WHO)'s technical guidance on COVID-19, including confirmation with reverse transcription polymerase chain reaction (RT-PCR) (9).

The COVID-19-related ARDS was diagnosed according to the Berlin criteria published in JAMA: "development of acute and bilateral pulmonary infiltrates and hypoxemia ($\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg or $\text{SpO}_2/\text{FiO}_2 \leq 315$ as a surrogate if no PaO_2 data are available in the study) not primarily due to heart failure or volume overload" (10). In the cohort, the ARDS patients were diagnosed not considering their positive end-expiratory pressure (PEEP) in order to identify the risk factors for the intubation or death earlier. Patients were screened and included by reviewing their electronic medical records and laboratory results. We excluded COVID-19 patients who were not confirmed by the RT-PCR testing, or pneumonia caused by other pathogens, such as bacteria, fungi, mycoplasma or chlamydia.

The study was approved by the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20200113), and the requirement for informed consent was waived because of the retrospective study design. All methods were performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (11).

Data collection

We reviewed the electronic medical records, laboratory results and radiographic reports of all admitted COVID-19 patients. Using a modified version of the standardized case report form developed by the International Severe Acute Respiratory and Emerging Infection Consortium and WHO (12), we extracted data on the demographic characteristics, medical history, comorbidities, illness onset date, initial symptoms, vital signs on admission and other data such as the severity of pneumonia graded by physicians. We also extracted the results of routine hematological, biochemical and inflammation-related indices obtained within 72 hours of hospital admission. treatments (antiviral drugs, antibiotics, glucocorticoids and vasopressor agents) or advanced therapies (intensive care unit (ICU) care, continuous renal-replacement therapy (CRRT), prone position ventilation and extracorporeal membrane oxygenation (ECMO); complications with death and other clinical outcomes. Further,

we collected information on ARDS diagnosis, including chest imaging; FiO_2 , PaO_2 or SpO_2 values to calculate oxygenation index (OI); oxygen supplement modalities; intubation date; IMV duration; Reports of chest radiographs were obtained, and any factors associated with ARDS and acute respiratory failure warranting intubation in the cohort or with death were recorded.

Outcomes

The outcomes were ARDS development and intubation or death at hospital.

Statistical analysis

Continuous data are expressed as medians with interquartile ranges (IQRs). Categorical data are presented as counts (n) with percentages (%). Missing data were not imputed. We used Kruskal-Wallis rank test and Fisher's exact test to compare the results between ARDS and non-ARDS patients of COVID-19, and between ARDS patients who were never intubated and those who were intubated. Bivariate cox proportional hazard ratio (HR) models were used to determine HRs and 95% CIs for the risk factors associated with the ARDS or the development from ARDS to intubation/death. Sensitivity analysis yielding adjusted HRs for the popular concerned predictors of lymphopenia and oxygenation index ratio less than 150 were conducted by using multivariate cox proportional HR model. Due to the explorative nature of the study, no formal hypotheses and the sample size calculation were proposed, and we included the maximum number of COVID-19 patients from the two hospitals. *P* values less than 0.05 were considered significant. All analyses were performed in SPSS (version 25, IBM Corp, Armonk, NY, USA) and Stata (version 16; Stata Corp, College Station, TX, USA) and RStudio (Version 1.3.1056, R Foundation for Statistical Computing).

Results

Demographics, characteristics, and clinical outcomes

From 26 January to 1 April 2020, 338 patients with COVID-19 confirmed by laboratory findings or otherwise clinical diagnosis were treated at the two hospitals in Hubei province of China. We included 333 patients, of which 65 subjects developed ARDS, and we excluded 5 cases due to negative/no laboratory testing or insufficient data. The details of enrolment are provided in Fig. 1.

Compared with patients without ARDS, patients with ARDS were older ($P < 0.001$) and trended higher BMI ($P = 0.055$), and more patients with ARDS were over 65 years ($P = 0.015$) and males ($P = 0.008$) (Table 1). Median days from symptoms onset to hospital admission were shorter in ARDS than non-ARDS patients ($P = 0.012$). However, more patients with ARDS presented with initial symptoms of fever ($P = 0.028$), cough ($P = 0.009$), fatigue ($P = 0.050$), expectoration ($P < 0.001$), palpitation and chest distress ($P < 0.001$), and at least three symptoms ($P < 0.001$) compared with those who did not develop ARDS. Patients who progressed into ARDS had higher breath rate ($P = 0.008$), more comorbidities ($P = 0.008$), and severest pneumonia graded by physicians ($P = 0.008$) on admission than patients not progressing into ARDS. All subjects were found to have bilateral infiltrate in lung in the severe illness of COVID-19 compared to 15.2% in the non-severe patients ($P < 0.001$). For treatment, the significantly higher percentages of patients with ARDS received general or advanced therapies, including antiviral therapy ($P = 0.002$), antibiotic ($P < 0.001$), glucocorticoid ($P < 0.001$), ICU-level care ($P < 0.001$), prone positioning ($P < 0.001$), CRRT ($P < 0.001$), and ECMO ($P < 0.001$). At last, when compared with patients who

did not happen ARDS, patients with the severe illness further progressed more on IMV due to failure of noninvasive respiratory support ($P < 0.001$), stayed longer in hospital ($P = 0.012$), and died more ($P < 0.001$). No patient in non-ARDS group occurred severe complications compared to the 13 in ARDS group had acute respiratory failure ($P < 0.001$) and acute circulatory failure ($P < 0.001$), and the 7 occurred Shock/MODS ($P < 0.001$).

Table 1

Characteristics and outcomes between COVID-19 patients with ARDS and without ARDS and between the ARDS subgroup of intubation and never intubation

Study variables	All patients			Patients with ARDS		
	Value, no./total no. (%) or median (IQR) (n = 333)			Value, no./total no. (%) or median (IQR) (n = 65)		
	Without ARDS (n = 268)	With ARDS (n = 65)	P value	Intubation (n = 20)	Never Intubation (n = 45)	P value
Age						
median, IQR	59.0 (43.0–68.0)	67.0 (56.0–78.0)	< 0.001	71.5 (65.5–79.5)	61.0 (55.0–77.0)	0.094
≥ 65 years	100/268 (37.3%)	35/65 (53.8%)	0.015	15/20 (75.0%)	19/45 (42.2%)	0.015
Male sex	141/268 (37.3%)	46/65 (70.8%)	0.008	12/20 (60.0%)	34/45 (75.6%)	0.203
BMI*						
median, IQR	23.4 (21.5–25.5)	24.4 (22.4–26.7) (n = 52)	0.055	23.5 (21.5–27.2) (n = 18)	24.6 (23.4–26.7) (n = 32)	0.538
≥ 25	86/268 (32.1%)	21/52 (40%)	0.246	7/18 (38.9%)	13/32 (40.6%)	0.904
Smoke history	22/268 (8.2%)	7/65 (10.8%)	0.511	2/20 (10%)	5/45 (11.1%)	1.000
Alcohol used	23/268 (8.6%)	9/65 (13.8%)	0.196	1/20 (5%)	8/45 (17.8%)	0.255
Days from symptoms onset to hospital admission (median, IQR)	10.0 (5.0–15.0)	8.0 (5.0–10.0)	0.012	7.5 (5.0–10.0)	9.0 (5.0–11.0)	0.383
Initial symptoms						
Fever	191/268 (71.3%)	55/65 (84.6%)	0.028	18/20 (90.0%)	37/45 (82.2%)	0.711
Cough	142/268 (53.0%)	46/65 (70.8%)	0.009	15/20 (75.0%)	31/45 (68.9%)	0.617

* Data regarding the BMI were missing for 28 of 333 patients (8.4%).

† All patients first were on noninvasive oxygen support when admitted at hospital.

‡ Data summarized from the patients admitted into ICU.

Abbreviations: IQR, interquartile range, OI: Oxygenation Index, ECMO: Extracorporeal membrane oxygenation, MODS: Multiple Organ Dysfunction Syndrome.

Study variables	All patients			Patients with ARDS		
	Value, no./total no. (%) or median (IQR) (n = 333)			Value, no./total no. (%) or median (IQR) (n = 65)		
Short of breath	142/268 (53.0%)	27/65 (41.5%)	0.098	12/20 (60.0%)	17/45 (37.8%)	0.096
Fatigue	56/268 (20.9%)	21/65 (32.3%)	0.050	11/20 (55.0%)	10/45 (22.2%)	0.009
Expectoration	41/268 (15.3%)	17/65 (26.2%)	< 0.001	7/20 (35.0%)	10/45 (22.2%)	0.279
Palpitation and chest distress	23/268 (8.6%)	17/65 (26.2%)	< 0.001	7/20 (35.0%)	10/45 (22.2%)	0.279
Number of complaints $\geq$ 3	113/268 (42.2%)	44/65 (67.7%)	< 0.001	18/20 (90.0%)	26/45 (57.8%)	0.011
Vital signs on admission fever ($\geq$ 37.2°C)						
Breath rate (median, IQR)	19.0 (18.0–20.0)	20.0 (20.0–24.0)	0.008	20.0 (20.0–22.0)	21.0 (20.0–24.0)	0.641
Heart rate (median, IQR)	90.0 (80.0–108.0)	85.0 (79.0–99.0)	0.340	88.0 (80.0–106.0)	85.0 (79.0–96.0)	0.889
SBP (median, IQR)	126.5 (117.5–137.0)	135.0 (120.0–141.0)	0.249	145.5 (140.0–154.0)	124.0 (116.0–135.0)	0.004
DBP (median, IQR)	79.5 (70.0–87.5)	79.0 (71.0–86.0)	0.849	85.0 (84.0–86.0)	76.0 (70.0–84.0)	0.131
MAP (median, IQR)	96.0 (86.7–102.0)	99.3 (86.7–105.0)	0.360	103.5 (101.3–115.7)	94.7 (86.7–101.0)	0.021
Severity of pneumonia graded by physicians						
Mild	28/260 (10.8%)	2/65 (3.1%)		0/20 (0.0%)	2/45 (4.4%)	
Severe	212/260 (81.5%)	18/65 (27.7%)		3/20 (15.0%)	15/45 (33.3%)	
Critical	20/260 (7.7%)	45/65 (68.3%)	< 0.001	17/20 (85.0%)	28/45 (62.2%)	0.217

* Data regarding the BMI were missing for 28 of 333 patients (8.4%).

† All patients first were on noninvasive oxygen support when admitted at hospital.

‡ Data summarized from the patients admitted into ICU.

Abbreviations: IQR, interquartile range, OI: Oxygenation Index, ECMO: Extracorporeal membrane oxygenation, MODS: Multiple Organ Dysfunction Syndrome.

Study variables	All patients			Patients with ARDS		
	Value, no./total no. (%) or median (IQR) (n = 333)			Value, no./total no. (%) or median (IQR) (n = 65)		
Comorbidities						
Hypertension	91/268 (40.0%)	20/65 (30.8%)	0.625	9/20 (45.0%)	11/45 (24.4%)	0.314
Diabetes	36/268 (13.4%)	10/65 (15.4%)	0.682	3/20 (25.0%)	7/45 (15.6%)	1.000
Brain disease	8/268 (3.0%)	6/65 (9.2)	0.024	1/20 (5.0%)	5/45 (11.1%)	0.657
Cardiovascular disease	27/268 (10.1%)	8/65 (12.3%)	0.598	1/20 (5.0%)	7/45 (15.6%)	0.417
Chronic lung disease	1/268 (0.38%)	2/65 (3.1%)	0.099	0/20 (0.0%)	2/45 (4.4%)	1.000
Number of coexisting disorders ≥ 1	12/268 (4.5%)	44/65 (67.7%)	< 0.001	14/20 (70.0%)	30/45 (66.7%)	0.791
Days from hospital admission to ARDS diagnosis (median, IQR)	NA	1.0 (0.0–4.0)		1.0 (0.0–4.0)	1.0 (0.0–5.0)	0.823
Days from symptoms onset to ARDS diagnosis (median, IQR)	NA	11.0 (8.0–13.0)		10.5 (6.5–12.5)	11.0 (8.0–15.0)	0.275
Chest imaging, bilateral infiltrate	40/264 (15.2%)	65/65 (100%)	< 0.001	20/20 (100%)	45/45 (100%)	1.000
Oxygenation Index on ARDS Diagnosis						
median (IQR)	NA	182.9 (134.0–225.0)		140.8 (119.9–189.2)	200.0 (158.0–247.5)	0.004
300 – 200	NA	24/63 (38.1%)		4/20 (20.0%)	23/45 (51.1%)	
199 – 100	NA	32/63 (50.8%)		12/20 (60.0%)	19/45 (42.2%)	
< 100	NA	7/63 (11.1%)		4/20 (20.0%)	3/45 (6.7%)	0.033
* Data regarding the BMI were missing for 28 of 333 patients (8.4%).						
† All patients first were on noninvasive oxygen support when admitted at hospital.						
‡ Data summarized from the patients admitted into ICU.						
Abbreviations: IQR, interquartile range, OI: Oxygenation Index, ECMO: Extracorporeal membrane oxygenation, MODS: Multiple Organ Dysfunction Syndrome.						

Study variables	All patients			Patients with ARDS		
	Value, no./total no. (%) or median (IQR) (n = 333)			Value, no./total no. (%) or median (IQR) (n = 65)		
Treatments						
Antiviral therapy	220/268 (82.1%)	63/65(95.2%)	0.002	20/20 (100%)	43/45 (95.3%)	1.000
Intravenous antibiotic	82/268 (48.8%)	60/65 (92.3%)	< 0.001	20/20 (100%)	40/45 (88.4%)	0.313
Glucocorticoid (methylprednisolone)	12/268 (4.5%)	51/65 (7.8.5%)	< 0.001	20/20 (100%)	31/45 (67.4%)	0.003
Vasopressor	0/268 (0.0%)	16/65 (24.6%)	< 0.001	10/20 (50.0%)	6/45 (14.0%)	0.002
Admission to ICU	7/268 (2.6%)	29/65 (44.6%)	< 0.001	15/20 (75.0%)	14/45 (27.9%)	0.012
Prone positioning	0/268 (0.0%)	8/65 (12.3%)	< 0.001	8/20 (40.0%)	0/45 (0.0%)	< 0.001
Continuous renal-replacement therapy	0/268 (0.0%)	6/65 (9.2%)	< 0.001	6/20 (30.0%)	0/45 (0.0%)	< 0.001
ECMO	0/268 (0.0%)	4/65 (6.2%)	< 0.001	5/20 (25.0%)	0/45 (0.0%)	0.002
Outcomes						
Failure of noninvasive respiratory support†	0/268 (0.0%)	20/65 (31.7%)	< 0.001	20/20 (100%)	0/45 (0.0%)	< 0.001
Median ICU stay (day, IQR)‡	7.0 (6.0–12.0)	15.0 (10.0–20.0)	0.075	16.0 (10.0–21.0)	11.0 (4.0–16.0)	0.131
Median Hospital stay (day, IQR)	17.0 (12.0–24.0)	22.0 (13.0–34.0)	0.012	25.0 (16.0-35.5)	22.0 (12.0–31.0)	0.227
Death in hospital	0/268 (0.0%)	24/65 (36.9%)	< 0.001	14/20 (70.0%)	10/45 (22.2%)	< 0.001
Death of mild ARDS	NA	5/26 (19.2%)		3/4 (75.0%)	2/23(8.7%)	0.013
Death of moderate ARDS	NA	13/32 (40.6%)		7/12(58.3%)	6/19(31.6%)	0.141
Death of severe ARDS	NA	6/7 (85.7%)		4/4(100.0%)	2/3(66.7%)	0.429
* Data regarding the BMI were missing for 28 of 333 patients (8.4%).						
† All patients first were on noninvasive oxygen support when admitted at hospital.						
‡ Data summarized from the patients admitted into ICU.						
Abbreviations: IQR, interquartile range, OI: Oxygenation Index, ECMO: Extracorporeal membrane oxygenation, MODS: Multiple Organ Dysfunction Syndrome.						

Study variables	All patients			Patients with ARDS		
	Value, no./total no. (%) or median (IQR) (n = 333)			Value, no./total no. (%) or median (IQR) (n = 65)		
Complications						
Acute respiratory failure	0/268	13/65 (20.0%)	< 0.001	5/20 (25.0%)	2/45 (4.4%)	0.025
Acute circulatory failure	0/268	13/65 (20.0%)	< 0.001	7/20 (35.0%)	6/45 (13.3%)	0.044
Shock/MODS	0/268	7/65 (10.8%)	< 0.001	5/20 (25.0%)	2/45 (4.4%)	0.025
* Data regarding the BMI were missing for 28 of 333 patients (8.4%).						
† All patients first were on noninvasive oxygen support when admitted at hospital.						
‡ Data summarized from the patients admitted into ICU.						
Abbreviations: IQR, interquartile range, OI: Oxygenation Index, ECMO: Extracorporeal membrane oxygenation, MODS: Multiple Organ Dysfunction Syndrome.						

In the subgroup of COVID-19 patients with ARDS, more patients who progressed on IMV were over 65 years ($P = 0.015$), reported fatigue ($P = 0.009$) and at least three symptoms at admission ($P = 0.011$), and had higher SBP ($P = 0.004$) or MAP levels ($P = 0.021$) with admission fever compared with patients who were never intubated (Table 1). The median oxygenation index of intubation patients at ARDS diagnosis were 140.8 (IQR, 119.9-189.2) compared to 200.0 (IQR, 158.0-247.5) of patients without intubation ($P = 0.004$), and higher percentage of intubation patients presented with moderate or severe ARDS at first than patients not on intubation ($P = 0.033$). In addition, patients intubated were more likely to be treated with glucocorticoid ($P = 0.003$) and admitted into ICU ($P = 0.012$), and to receive prone positioning ($P < 0.001$), CRRT ($P < 0.001$), or ECMO ($P = 0.002$) comparing with patients not intubated during hospitalization. A higher proportion of patients intubated developed acute respiratory ($P = 0.025$), circulatory failure ($P = 0.044$), Shock/MODS ($P = 0.025$), and finally died in hospital ($P < 0.001$). The morality rate was particularly higher in the mild ARDS who received IMV ($P = 0.013$) than those did not.

Laboratory indices tested at admission found that compared with patients without ARDS, for patients with ARDS, the value of liver damage indices (AST $P = 0.003$, ALT $P = 0.024$, Albumin $P < 0.001$, A/G $P < 0.001$), heart injury indices (LDH and cTnI $P < 0.001$), pancreas injury indices (glucose $P < 0.001$) inflammation-related indices (ESR, CRP and PCT $P < 0.001$), coagulation function indices (D-Dimer, PT and INR $P < 0.001$), kidney dysfunction indices (CRE and GFR $P < 0.001$) and blood sodium levels were elevated ($P < 0.001$) (Table 2). However, in ARDS patients, blood cell counts of WBC ($P < 0.001$), neutrophil ($P < 0.001$) and lymphocyte ($P < 0.001$) and potassium levels ($P = 0.041$) were significantly decreased. ARDS patients demonstrated immune system destruction indicated by extremely lower median values of lymphocyte count per mm³ (670, IQR 430–1040) and multiple organ injuries suggested by abnormal median values of A/G ratio (1.13, IQR 0.95–1.39), LDH (371.5, IQR 227.0–519.0), blood glucose (7.9, IQR 6.0–10.5), and D-Dimer (0.6, IQR 0.2–2.4) levels. In the subgroup analysis, there was no significant difference of laboratory indices between the patients intubated and the patients never

intubated. Nevertheless, ARDS patients on IMV trended lower cell counts of WBC, neutrophil, and lymphocyte, and elevated markers related to the damages of liver, pancreas, and kidney than the patients never intubated.

Table 2

Initial laboratory indices between COVID-19 patients with ARDS and without ARDS and between the ARDS subgroup of intubation and never intubation

Laboratory indices on admission	All patients		ARDS			
	Without ARDS Value, median (IQR)	With ARDS Value, median (IQR)	P value	Intubation	Never intubation	P value
Hematologic						
WBC count /mm ³	5300 (4200–6400)	7340 (4700–10700)	< 0.001	6450 (4350–101500.)	7340 (4810–11500)	0.418
Neutrophil count /mm ³	3280 (2380–4360)	6320 (3440–9150)	< 0.001	5170 (3365–8985)	6490 (3490–10590)	0.706
Lymphocyte count /mm ³	1260 (915–1665)	670 (430–1040)	< 0.001	635 (400–795)	740 (460–1080)	0.149
Platelet count /mm ³	202 (157–256)	199 (146–236)	0.259	211 (119–223)	197 (154–261)	0.491
Hemoglobin, g/dL	12.6 (11.6–13.7)	13.1 (11.6–14.0)	0.185	13.0 (11.7–13.7)	13.2 (11.6–14.6)	0.367
Biochemical						
TBIL, µmol/L	11.6 (8.6–14.9)	13 (10.1–18.3)	0.069	15.0 (11.1–17.7)	12.0 (9.8–18.3)	0.323
AST, U/L	27.0 (22.0–38.5)	39.0 (25.0–50.0)	0.002	37.5 (26.5–50.0)	39.0 (23.0–50.0)	0.793
ALT, U/L	22.0 (15.0–36.0)	27.0 (20.0–35.0)	0.024	25.0 (18.0–29.0)	28.0 (20.0–43.0)	0.176
Total protein, g/L	64.7 (61.2–70.5)	64.0 (60.7–68.3)	0.156	64.8 (63.0–68.5)	62.6 (59.9–68.3)	0.179
Albumin, g/L	39.2 (35.8–41.7)	34.1 (31.2–37.5)	< 0.001	34.2 (30.5–36.9)	34.1 (31.3–38.0)	0.994

* Data regarding the cTnI were missing for 2 ARDS patients who were never intubated.

† Data regarding the Glucose were missing for 1 ARDS patient who were never intubated.

‡ Data regarding both the Potassium and Sodium were missing for 6 ARDS patients, with 4 at never intubation group, 1 at early intubation group, and 1 at late intubation group.

§ Data regarding the PTs were missing for 1 ARDS patient who were never intubated.

|| Data regarding the ESR were missing for 6 ARDS patients who were never intubated.

Abbreviations: IQR, interquartile range, WBC: White Blood Cell; TBIL: Total bilirubin, AST: aspartate transaminase, ALT: alanine aminotransaminase, LDH: lactate dehydrogenase, GFR: glomerular filtration rate, PT: prothrombin time, INR: international normalized ratio, ESR: Erythrocyte Sedimentation Rate.

Laboratory indices on admission	All patients			ARDS		
Albumin/Globulin	1.49 (1.27–1.66)	1.13 (0.95–1.39)	< 0.001	1.13 (0.86–1.25)	1.16 (0.96–1.39)	0.344
LDH, unit/L	210.0 (171.0–266.0)	371.5 (227.0–519.0)	< 0.001	384.0 (218.0–519.0)	361.0 (241.0–525.0)	0.927
cTnI, ng/mL*	0.01 (0.01–0.01)	0.02 (0.01–0.04)	< 0.001	0.02 (0.01–0.03)	0.01 (0.01–0.06)	0.953
Glucose, mmol/L†	5.8 (5.2–6.7)	7.9 (6.0–10.5)	< 0.001	7.8 (6.1–10.2)	7.9 (6.0–10.7)	0.739
Creatinine, µmol/L	65.0 (53.0–76.0)	74.2 (59.0–93.0)	< 0.001	74.4 (66.5–107.5)	74.2 (57.0–92.5)	0.685
GFR, ml/min/1.73m ²	100.0 (89.0–113.0)	89.0 (62.0–104.0)	< 0.001	72.5 (60.0–94.5)	93.0 (68.0–108.0)	0.120
Potassium, mmol/L‡	3.8 (3.5–4.1)	3.9 (3.7–4.3)	0.041	4.0 (3.7–4.1)	3.9 (3.6–4.3)	0.967
Sodium, mmol/L‡	140.6 (138.8–142.3)	137.8 (134.8–139.3)	< 0.001	137.6 (135.0–139.3)	137.9 (134.8–139.3)	0.882
D-Dimer, mg/L	0.1 (0.1–0.3)	0.6 (0.2–2.4)	< 0.001	0.4 (0.2–2.3)	0.7 (0.2–2.4)	0.776
PT, s§	11.8 (11.3–12.6)	13.1 (11.9–14.7)	< 0.001	13.1 (11.7–13.9)	13.2 (12.2–14.8)	0.339
INR	1.1 (1.0–1.2)	1.1 (1.1–1.2)	< 0.001	1.2 (1.1–1.2)	1.1 (1.1–1.2)	0.438
ESR, mm/h	22.0 (11.0–50.0)	62.5 (31.0–81.0)	< 0.001	66.5 (30.5–84.5)	60.5 (39.0–80.0)	0.832
C-Reactive Protein, mg/L	10.0 (3.5–26.3)	59.1 (20.1–108.6)	< 0.001	72.0 (38.2–110.6)	48.2 (19.5–108.6)	0.410
Procalcitonin, µg/L	0.04 (0.03–0.07)	0.12 (0.05–0.38)	< 0.001	0.21 (0.07–0.50)	0.10 (0.05–0.35)	0.438
* Data regarding the cTnI were missing for 2 ARDS patients who were never intubated.						
† Data regarding the Glucose were missing for 1 ARDS patient who were never intubated.						
‡ Data regarding both the Potassium and Sodium were missing for 6 ARDS patients, with 4 at never intubation group, 1 at early intubation group, and 1 at late intubation group.						
§ Data regarding the PTs were missing for 1 ARDS patient who were never intubated.						
Data regarding the ESR were missing for 6 ARDS patients who were never intubated.						
Abbreviations: IQR, interquartile range, WBC: White Blood Cell; TBIL: Total bilirubin, AST: aspartate transaminase, ALT: alanine aminotransaminase, LDH: lactate dehydrogenase, GFR: glomerular filtration rate, PT: prothrombin time, INR: international normalized ratio, ESR: Erythrocyte Sedimentation Rate.						

High mortality of COVID-19 ARDS patients with intubation and the initial time of intubation

COVID-19 ARDS patients requiring intubation showed a high mortality at 70.0% (Table 1). However, we found the survivors had been intubated earlier since ARDS diagnosis than the non-survivors, with a median of 5.5 and IQR of 4.0–7.0 days versus a median of 11.5 and IQR 6.0–14.0 days ($P < 0.001$) (Fig. 2).

Risk factors associated with ARDS and intubation/death in COVID-19 patients

Univariate cox proportion hazard models showed that age and age over 65 years were associated with the development of ARDS (HR, 1.04; 95% CI, 1.01–1.06, HR, 2.24; 95% CI, 1.18–4.28) and the intubation/death (HR, 1.03; 95% CI, 1.01–1.06, HR, 3.07; 95% CI, 1.32–7.16) (Table 3). Other factors including male gender and abnormal laboratory indices related to the development of ARDS were not found to be associated with the intubation/death. However, the number of symptom complaints equal and more than three was associated with higher likelihood of progressing into intubation/death (HR, 4.74; 95% CI, 1.65–13.66). Patients on lower OI ratio at ARDS diagnosis (HR, 0.99; 95% CI, 0.98–1.00) and patients with OI ratio less than 200 (HR, 3.05; 95% CI, 1.24–7.46), 150 (HR, 3.00; 95% CI, 1.45–6.17), or 100 (HR, 2.54; 95% CI, 1.03–6.25) were more likely to require intubation or die in hospital. Sensitivity analysis showed that when adjusting for age and gender, COVID-19 patients with lymphocyte count of < 1000 per mm^3 at admission were still significantly associated with developing ARDS (HR, 4.10; 95% CI, 2.40–7.10). When adjusting for age, ARDS patients with lower OI ratio less than 150 at ARDS diagnosis were also more likely to need the intubation or happen the death (HR, 2.50; 95% CI, 1.17–5.30) (Table S1).

Table 3
Risk factors associated with ARDS and ARDS progressing on Intubation or Death

Variables	ARDS (n = 65)		Intubation or Death (n = 30)	
	HR (95% CI)	P value	HR (95% CI)	P value
Clinical characteristics				
Age	1.04 (1.01–1.06)	0.001	1.03 (1.01–1.06)	0.019
Age (≥ 65) years	2.24 (1.18–4.28)	0.014	3.07 (1.32–7.16)	0.009
Gender (male vs female)	2.08 (1.03–4.20)	0.040	0.70 (0.32–1.49)	0.352
Number of complaints (≥ 3)	1.50 (0.77–2.95)	0.236	4.74 (1.65–13.66)	0.004
Hypertension	1.03 (0.53–2.02)	0.928	1.61 (0.77–3.35)	0.204
Number of coexisting disorders (≥ 1)	1.15 (0.57–2.36)	0.693	1.82 (0.74–4.50)	0.192
Oxygenation Index				
Values	NA	NA	0.99 (0.98–1.00)	0.001
< 200	NA	NA	3.05 (1.24–7.46)	0.015
< 150	NA	NA	3.00 (1.45–6.17)	0.003
< 100	NA	NA	2.54 (1.03–6.25)	0.042
Laboratory findings				
Lymphocyte count /mm ³ (< 1000)	4.72 (2.34–9.51)	< 0.001	1.58 (0.64–3.87)	0.319
Albumin, g/L (< 32)	3.36 (1.70–6.66)	0.001	0.88 (0.38–2.07)	0.775
Albumin/Globulin (< 1.5)	10.02 (3.08–32.60)	< 0.001	0.89 (0.34–2.34)	0.818
LDH, unit/L (> 280)	5.44 (2.78–10.64)	< 0.001	1.10 (2.51 – 0.35)	0.810
cTnI, ng/mL (> 0.04)	3.80 (1.91–7.55)	< 0.001	0.84 (0.36–1.95)	0.678
Glucose, mmol/L (> 7.1)	4.33 (2.27–8.25)	< 0.001	1.46 (0.64–2.92)	0.425
Creatinine, μ mol/L (> 110)	3.88 (1.62–9.31)	0.002	0.54 (0.19–1.54)	0.247

* Data regarding the cTnI were missing for 2 ARDS patients who were dead.

† Data regarding the Glucose were missing for 1 ARDS patient who were never intubation or not dead.

‡ Data regarding the PTs were missing for 1 ARDS patient who were never intubated or not dead.

§ Data regarding the ESR were missing for 6 ARDS patients who were never intubated or not dead.

Abbreviations: HR; hazard ratio; WBC: White Blood Cell; TBIL: Total bilirubin, AST: aspartate transaminase, ALT: alanine aminotransaminase, LDH: lactate dehydrogenase, GFR: glomerular filtration rate, PT: prothrombin time, INR: international normalized ratio, ESR: Erythrocyte Sedimentation Rate.

Variables	ARDS (n = 65)		Intubation or Death (n = 30)	
GFR, ml/min/1.73m ² (< 80)	3.64 (1.91–6.93)	< 0.001	1.18 (0.58–2.43)	0.648
Sodium, mmol/L (< 135)	3.84 (1.90–7.75)	< 0.001	0.88 (0.38–2.05)	0.766
D-Dimer, mg/L (> 0.5)	3.99 (2.10–7.57)	< 0.001	0.81 (0.39–1.67)	0.569
PT, s (> 13.5)	5.55 (2.93–10.49)	< 0.001	0.69 (0.33–1.46)	0.337
INR (> 1.1)	10.02 (3.08–32.60)	< 0.001	1.18 (0.56–2.47)	0.659
ESR, mm/h (> 20)	6.80 (2.09–22.12)	0.001	1.33 (0.32–5.60)	0.696
C-Reactive Protein, mg/L (> 10)	7.47 (2.92–19.1)	< 0.001	0.71 (0.25–2.06)	0.533
Procalcitonin, µg/L (> 0.1)	4.39 (2.32–8.30)	< 0.001	0.74 (0.36–1.52)	0.418
* Data regarding the cTnI were missing for 2 ARDS patients who were dead.				
† Data regarding the Glucose were missing for 1 ARDS patient who were never intubation or not dead.				
‡ Data regarding the PTs were missing for 1 ARDS patient who were never intubated or not dead.				
§ Data regarding the ESR were missing for 6 ARDS patients who were never intubated or not dead.				
Abbreviations: HR; hazard ratio; WBC: White Blood Cell; TBIL: Total bilirubin, AST: aspartate transaminase, ALT: alanine aminotransaminase, LDH: lactate dehydrogenase, GFR: glomerular filtration rate, PT: prothrombin time, INR: international normalized ratio, ESR: Erythrocyte Sedimentation Rate.				

Discussion

In this study, we observed that the ARDS caused by COVID-19 was not the typical ARDS defined by the Berlin criteria due to more than 1-week onset time, multiple organs injuries, and higher mortality. We found that the survivors who were on IMV had been intubated earlier since ARDS diagnosis than the non-survivors. We reported the different risk factors between COVID-19 patients who developed ARDS after admission and who progressed from ARDS to intubation or death.

Older age or age over 65 years was the most consistently reported risk factors for patients who develop ARDS, as concluded by previous investigations (13). Interestingly, we found the hazards ratio of age over 65 years associated with the intubation or death was larger than the ratio of this factor with ARDS, which suggests that the risk for worse clinical outcomes markedly increased once the elder patients developed ARDS. The reason could be the accelerating decline of immune response (14, 15). To prevent the ARDS development for the elder patients shall reduce the worse outcomes. Another different finding compared with the studies published was that males faced a significantly greater risk of developing ARDS. However, for the typical ARDS caused by other factors, females were found to be more likely to develop the disease than males (16). One possible explanation was the protection of X chromosome and sex hormones which played an important role in innate and adaptive immunity made the females less susceptible to coronavirus infection than men, resulting in the less development of the critical disease (17).

The two-hospital cohort found that the COVID-19 subjects with abnormal laboratory indices at admission were more possibly to progress into ARDS. The lymphopenia, which is defined as the counts less than 1000 counts/mm³, strongly predicted the ARDS for COVID-19 patients. Even adjusting for age and male gender, the lymphopenia was associated with fourfold risk of ARDS. Lymphocytes express the ACE2 receptor and may be a direct target of SARS-CoV-2 infection, and an increase of pro-inflammatory cytokines in COVID-19, especially IL-6, could induce further lymphocyte reduction (18). When the patient's laboratory indicator showed PCT > 0.1 ng/mL, ESR > 20 mm/h or C-Reactive Protein > 10 mg/L, there was a higher risk of progression to the critical illness. That may support the corticosteroids use to prevent the risk of ARDS, particularly for the elder patients, due to alleviating the systemic inflammation (19). The positive associations between albumin < 32 g/L, LDH > 280U/L, cTnI, ng/mL > 0.04, creatinine > 110 µmol/L or glucose > 7.1 mmol/L and the ARDS indicated that the liver, heart, kidney or pancreas dysfunctions had been involved, and corresponding therapies should be taken in time to prevent the further deterioration of the COVID-19. When the D-dimer > 0.5mg/L meant the high risk of the progression of the COVID-19 to ARDS, the approaches to alter the hypercoagulability of blood, reduce the risk of thrombosis, and improve the ischemia and hypoxia shall be implemented early (18).

No laboratory indicators predicting the need of intubation or death suggests different pathophysiological pathways between ARDS development and hypoxemic respiratory failure/death in COVID-19. The ARDS patients presenting with symptoms ≥ 3 were more likely to be intubated or die at hospital. The clinicians might monitor these ARDS patients more closely to implement therapies in time even though the patients did not suffer any co-existing disease. Additionally, the analysis revealed that COVID-19 patients with lower OI ratios at ARDS diagnosis were more likely to develop hypoxemic respiratory failure necessitating IMV and had higher risk to die. The COVID-19 Guidelines of Europe (20), USA (21), and Canada (22) have not yet provided any recommendation related to intubation. Our findings that the decreasing OI ratio in ARDS patients was highly associated with hypoxemic respiratory failure necessitating the intubation and the risk of in-hospital death may supported the early intubation criteria of the COVID-19 Management — patients with an SpO₂ value of less than 93% of the room air and a OI ratio of less than 300 mmHg should be prepared for intubation if there are indications (23). The sensitivity analysis showed that the OI ratio less than 150 well predicted the need of intubation and death when adjusting for age. The threshold might be considered as a caution to the deterioration of COVID-19 patients to facilitate the early treatment.

The study complements the existing small studies on the clinical features of ARDS caused by COVID-19 with a comparably large sample. The longer median onset days (11.0, IQR, 8.0–13.0), which exceeds 1-week limit of typical ARDS (10), should alert physicians to monitor the COVID-19 patients longer for adequate treatment. The mortality rates of moderate and severe COVID-19 ARDS were higher than the corresponding data of 32% and 45% of the typical ARDS (24). One possible explanation we thought is the silent hypoxemia that the patient had severe hypoxemia but was asymptomatic, which would lead to delay treatment (25, 26). Therefore, from the perspective of treatment, an adjusted classification of ARDS severity that can correctly identify COVID-19 patients who require a timely therapy for has been always needed (7). Most importantly, the ARDS caused by COVID-19 demonstrated injuries in multiple organs, including the heart, the liver, the kidney, and the pancreas, which was supported by the fundamental research that this new coronavirus can attack the tissues of other organs in addition to the respiratory tract (15). At the two-hospital cohort, 78.5% patients with ARDS were given systemic corticosteroids to alleviate hyperinflammation. However, guidance regarding corticosteroids use for COVID-19 is still mixed (27). Some issued a weak recommendation (28), but others issued a weak

recommendation against the use of corticosteroids for COVID-19 and ARDS (29). Nevertheless, the latest publication of three randomized trials of corticosteroids and the prospective meta-analysis have strengthened confidence and shifted usual care of COVID-19–related ARDS to include corticosteroids (27).

An interesting result in this cohort was that the survivors with IMV were intubated earlier than those with IMV who did not survive. We noticed the non-survivor group had the median intubation days at 11.5, which exceed one week after ARDS diagnosis or hospital admission. By contrast, we observed the patients intubated within one week after ICU admission or ARDS diagnosis demonstrated much lower mortalities in our cohort, in other hospitals of China (6), and some places of USA (30). To intubate the COVID-19 patients within one week since critical illness development seemed to result in a lower mortality rate. However, because we were not sure the two hospital used the same intubation criteria at that time, and we did not have the specific values when they were progressed into intubation, we could not say these ARDS patients had survived due to comparable early intubation. Even nowadays, the definition of what constitutes “early” is still a challenge and requires necessary investigations for COVID-19. As Shoemaker et al.’s study (23) highlights the importance of timely stopping an enlarging oxygen debt using effective oxygenation and ventilation therapies because there is a close association between the oxygen debt accumulated over 48 hour and the chance of survival in patients undergoing high-risk surgery and ICU admission afterward.

The strengths of the study are as follows: the study cohort included a comparably large sample size from two hospitals in two cities of Hubei province, which increases the robustness and generalizability of the findings; reported HRs for the risk factors and did the sensitivity analysis for the popular concerned risk factors associated with ARDS and ARDS progressing on IMV or death. However, the study has some limitations. First, owing to limited medical resources, only patients with relatively severe COVID-19 were hospitalized during this period. As such, this study may have included disproportionately more patients with poor outcomes. There may also be a selection bias when identifying factors that influence the clinical outcomes. Second, it is a retrospective cohort conducted at two hospitals. As is known, it was hard to perform a perspective cohort when pandemic happened and developed everywhere. As we have sparse new COVID-19 cases now, we hope our new findings can encourage a larger prospective cohort study or even randomly controlled trials in other regions who are experiencing the outbreak and in the urgent need to adjust the strategy.

Conclusions

In conclusion, the SARS-CoV-2-caused ARDS was not the typical ARDS for which the management strategies should be modulated accordingly. The survival patients had been intubated earlier since ARDS diagnosis than those who had not survived, which may propose the issue of timing of intubation. Lymphopenia predicted the ARDS and OI ratio less than 150 predicted the intubation/death. The male gender and all the abnormal laboratory indices associated with the ARDS but were not linked with the intubation or death, suggesting different pathophysiological processes at the two stages.

Abbreviations

COVID-19: coronavirus disease 2019; IMV: invasive mechanical ventilation; CFR: case fatality rate; OI: oxygenation index; CRRT: continuous renal-replacement therapy; ECMO: extracorporeal membrane oxygenation; WHO: World Health Organization; ICU: intensive care unit; PaO₂/FiO₂: arterial partial pressure of oxygen/fraction

of inspired oxygen; SpO₂/FiO₂: oxygen saturation by pulse oximetry/fraction of inspired oxygen; PEEP: positive end-expiratory pressure; RRs: risk ratios; IQR: interquartile range; CI: confidence intervals; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; BMI: body mass index; ESR: erythrocyte sedimentation rate; GFR: glomerular filtration rate; WBC: white blood cell; TBIL: total bilirubin; AST: aspartate transaminase; ALT: alanine aminotransaminase; LDH: lactate dehydrogenase; GFR: glomerular filtration rate; PT: prothrombin time; INR: international normalized ratio; ESR: erythrocyte sedimentation rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure

Declarations

Ethics approval and consent to participate

The study was approved by the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT20200113), and the requirement for informed consent was waived.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during and analyzed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request. A proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests.

Competing interests

We declare no competing interests.

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Author Contributions

JLM and KXL conceived the study and its design and take responsibility for the integrity of the data and accuracy of the analysis. JLM, MZQ, HMS, FZ, DSQ, HY, JN, and YHD organized and entered data. JLM, BSG, SDQ, FZ, HY, and XuD Liu contributed to data analyses. JLM, MZQ, BSG, XuDL, XiaoDL, WFY, BXL, YYS, ShYL, and KXL contributed to data interpretation. JLM and BSG drafted the manuscript. All authors critically revised the drafted manuscript and approve of the submitted manuscript.

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References

1. WHO. World Health Organization: Coronavirus Disease (COVID-19) Dashboard; 2020. Cited March 31 2021. Available from: <https://covid19.who.int/>.
2. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-20.
3. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory medicine*. 2020;8(5):475-81.
4. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *medRxiv : the preprint server for health sciences*. 2020.
5. C Carver NJ. Are there risk factors and preventative interventions for acute respiratory distress syndrome (ARDS) in COVID-19? : The Centre for Evidence-Based Medicine develops, promotes and disseminates better evidence for healthcare; 2020. Cited June 8 2020. Available from: <https://www.cebm.net/covid-19/are-there-risk-factors-and-preventative-interventions-for-acute-respiratory-distress-syndrome-ards-in-covid-19/>.
6. Wang T, Tang C, Chen R, Ruan H, Liang W, Guan W, et al. Clinical Features of Coronavirus Disease 2019 Patients With Mechanical Ventilation: A Nationwide Study in China. *Crit Care Med*. 2020;48:e809-e12.
7. Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS? *Critical care (London, England)*. 2020;24(1):198.
8. Fan E, Beitler JR, Brochard L, Calfee CS, Ferguson ND, Slutsky AS, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? *The Lancet Respiratory medicine*. 2020;8(8):816-21.
9. Novel coronavirus – China: World Health Organization; 2020. Cited March 31 2021. Available from: <http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>.
10. The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA*. 2012;307(23):2526-33.
11. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS medicine*. 2007;4(10):e297.
12. ISARIC WHO SARI Case Record Form: The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC); 2020. Cited May 5 2020. Available from: <https://isaric.tghn.org/>.
13. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. *JAMA Internal Medicine*. 2020;180(10):1345-55.
14. Wu C, Chen X, Cai Y, Xia Ja, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Internal Medicine*. 2020;180:1-11.

15. Chowdhury MA, Hossain N, Kashem MA, Shahid MA, Alam A. Immune response in COVID-19: A review. *Journal of Infection and Public Health*. 2020.
16. Heffernan DS, Dossett LA, Lightfoot MA, Fremont RD, Ware LB, Sawyer RG, et al. Gender and acute respiratory distress syndrome in critically injured adults: a prospective study. *J Trauma*. 2011;71(4):878-85.
17. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *J Infect*. 2020;81(2):e16-e25.
18. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. *Journal of Intensive Care*. 2020;8(1):36.
19. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *The Lancet Respiratory medicine*. 2020;8(3):267-76.
20. COVID-19 Guidelines: Society of Critical Care Medicine; 2020. Cited June 1 2020. Available from: <https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19>.
21. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: National Institutes of Health; 2020. Cited June 1 2020. Available from: <https://www.covid19treatmentguidelines.nih.gov/whats-new/>.
22. Clinical management of patients with moderate to severe COVID-19 - Interim guidance: Government of Canada; 2020. Cited July 28 2020. Available from: <https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/clinical-management-covid-19.html>.
23. Meng L, Qiu H, Wan L, Ai Y, Xue Z, Guo Q, et al. Intubation and Ventilation amid the COVID-19 Outbreak: Wuhan's Experience. *Anesthesiology: The Journal of the American Society of Anesthesiologists*. 2020;132(6):1317-32.
24. Fanelli V, Vlachou A, Ghannadian S, Simonetti U, Slutsky AS, Zhang H. Acute respiratory distress syndrome: new definition, current and future therapeutic options. *J Thorac Dis*. 2013;5(3):326-34.
25. Ottestad W, Seim M, Mæhlen JO. COVID-19 with silent hypoxemia. *Tidsskrift for den Norske lægeforening : tidsskrift for praktisk medicin, ny raekke*. 2020;140(7).
26. Nickson C IJ, Young P. "Silent hypoxaemia" and COVID-19 intubation: Life in the fastlane; 2020. Cited Feb 5 2021. Available from: <https://litfl.com/silent-hypoxaemia-and-covid-19-intubation/>.
27. Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: Evidence and Hope During the Pandemic. *JAMA*. 2020.
28. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e69.
29. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2020.
30. Suleyman G, Fadel RA, Malette KM, Hammond C, Abdulla H, Entz A, et al. Clinical Characteristics and Morbidity Associated With Coronavirus Disease 2019 in a Series of Patients in Metropolitan Detroit. *JAMA Network Open*. 2020;3(6):e2012270.

Figures

Figure 1

Flowchart of patient's enrolment

A

ARDS patients with intubation (n=20)

B

Figure 2

COVID-19 ARDS patients with intubation and the outcomes. A. Median (IQR) days from ARDS diagnosis to intubation between survival and dead patients; B. Outcomes of the patients receiving intubation; * $P < 0.05$. IQR, interquartile range.

Supplementary Files

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