

Clinical Characteristics and Outcomes of Patients with Coronavirus Disease 2019-associated ARDS and the Early Intubation: A Two-Hospital Retrospective Cohort Study in Hubei, China

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Abstract

Background: More evidence in understanding the heterogeneity of COVID-19-associated acute respiratory distress syndrome (ARDS) and in improving strategy to increase the survival from the critical patients intubated is always needed. The study aimed to comprehensively explore the features of COVID-19-associated ARDS and the features and outcomes between the early and late intubation groups.

Methods: This retrospective cohort included 65 adult COVID-19 inpatients with ARDS at two hospitals in Hubei, China. The ARDS in these patients was diagnosed according to the Berlin criteria. We defined intubation within 7 days of ARDS diagnosis as 'early' intubation and that performed from the eighth day as 'late' intubation based on literatures. The outcomes were invasive mechanical ventilation and in-hospital death. The log-binomial regression models were used to explore the risk factors and the Kaplan-Meier statistic was used to estimate the risk of mortality.

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 early intubation and the late intubation had the differences in days from symptom onset/hospital admission/ARDS diagnosis to intubation ($P = 0.023$, $P = 0.011$, $P < 0.001$). Compared with the early-intubation group, the late-intubation group showed less severity at admission (median oxygenation index 159.0 95% CI 134.0-203.0 vs. 133.9 95% CI 98.3-183.2), but required more aggressive therapies (ICU 80% vs. 70%, CRRT 50% vs. 10%, prone-position 50% vs. 30%, and ECMO 50% vs. 10%) and had higher risk to die at hospital (RR, 3.18; 95% CI 1.98-5.12).

Conclusion: The ARDS caused by COVID-19 was not typical ARDS due to prolonged onset time, multiple organ injuries, and higher mortalities. The late-intubation group showed less severity at admission but higher risk of in-hospital death than the early-intubation group.

Key Points

Question

Are features of ARDS caused by COVID-19 as similar as the previous ARDS? Is the late intubation at one week or later since ARDS diagnosis associated with the high mortality in COVID-19 patients compared to the early intubation?

Findings

In the retrospective cohort of 66 COVID-19 critical patients, we found that the ARDS was not the typically previous ARDS due to significantly prolonged onset time, multiple organ injuries, and higher mortalities. The late-intubation group showed less severity at admission but higher risk of in-hospital death compared with the early-intubation group.

Meaning

The findings had implications in modulating the management strategy for ARDS of COVID-19, and potentially in supporting the early or proactive intubation strategy.

Introduction

As of 27th February 2021, the coronavirus disease 2019 (COVID-19) pandemic has affected approximately 114 million people and caused over 2 million deaths worldwide [1]. The accumulated data suggest that 5–42% of COVID-19 patients develop severe illness that is characterized by acute respiratory distress syndrome (ARDS) [2, 3]. Our understanding about ARDS caused by COVID-19 remains remarkably different [4–6]. Some clinicians and researchers thought that the respiratory system mechanics of patients with ARDS, with or without COVID-19, were broadly similar [4], but others said that COVID-19-associated ARDS has distinctive features, including an primary vascular insult, that set it apart from previous ARDS and need to adjust the management strategies [5–7]. More evidence is always needed to clarify the features of ARDS to improve the treatment for the ongoing COVID-19 pandemic.

Another problem extremely required to be solved is the high mortality in COVID-19 patients who receive invasive mechanical ventilation (IMV) [8–10], which is the mainstay therapy for critical illness of COVID-19 [11, 12]. A systematic review [13] analyzed 69 studies with 121,009 COVID-19 patients and reported that the case fatality rate (CFR) (mortality) of the patients receiving IMV was 45% (95% CI 39–52%). For the patients who completed their hospital stay, and the definite CFR with IMV across 11 studies from China and 21 studies from USA was 69% (95% CI 48–90%) and 61% (95% CI 50–72%) respectively [13]. The mortality was even greater than 70% amongst patients aged above 60 years [13]. There are clinicians and researchers who think the timing of intubation is associated with the high mortality for COVID-19 patients [14, 15]. The invasive mechanical ventilation thus should be used as proactive but not salvage therapy, to reduce the deaths [7, 16]. There is a report that proposed the existence of two primary phenotypes of type L (low lung compliance) and type H (high lung compliance) of COVID-19-associated ARDS [7, 17]. Authors therefore advocated to perform proactive or early intubation in patients before excessive inspiratory efforts without worrying ventilator-induced lung injury as the high compliance results in tolerable strain [17]. Direct evidence on the consequences of delayed intubation in COVID-19 patients is not yet available. Early intubated patients seem to have better outcomes through personal experience. Analyses on retrospective data on this matter are urgently needed. In the studies published, there were a number of patients receiving intubation at one week or later after hospital admission compared with those receiving the therapy within one week [15, 18]. We therefore wonder if such comparably late intubation is associated with the high mortality.

We performed a two-centre retrospective cohort to extensively investigate the characteristics of COVID-19-associated ARDS patients, to explore the features and outcomes between the early and late intubation groups according to 1-week cutting point since ARDS diagnosis, and to study the predictors for the early intubation.

Materials And Methods

Ethical approval

This manuscript adheres to the applicable CONSORT guidelines. 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 and given the context of ongoing infectious diseases.

Study design

This retrospective cohort study included adult COVID-19 inpatients with ARDS (≥ 18 years old) from the General Hospital of Central Theatre Command of PLA in Wuhan (a tertiary hospital) and from the 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 real-time reverse transcription polymerase chain reaction (RT-PCR) [19].

Inclusion and exclusion criteria

We identified patients with COVID-19-related ARDS admitted to the two hospitals from 26 January 2020 to 1 April 2020. The ARDS was diagnosed according to the Berlin criteria: development of acute, bilateral pulmonary infiltrates (determined by chest imaging) 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 [20]. Patients with COVID-19-related ARDS were included in the cohort independent of their positive end-expiratory pressure (PEEP) requirements. Therefore, patients receiving oxygen via a nasal cannula and facemask were included if they met the criteria of ARDS, in order to recognize more potential inpatients who later presented with hypoxemia respiratory failure warranting IMV. Patients were screened and included by reviewing their electronic medical records and laboratory results. We excluded COVID-19 patients who did not meet the ARDS diagnosis criteria, who did not have laboratory confirmation of ARDS, or had ARDS caused by other pathogens, such as bacteria, fungi, mycoplasma or chlamydia.

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

Outcomes

The outcomes were intubation and mechanical ventilation and in-hospital death. Based on 1-week cut-off point, we defined intubation within 7 days of ARDS diagnosis as 'early' intubation and that performed from the eighth day as 'late' intubation. The patients were then classified into three categories: 1) 'early' intubation: IMV performed within 7 days of ARDS diagnosis, 2) 'late' intubation: IMV performed from the eighth day onwards since ARDS diagnosis, and 3) no intubation (non-invasive respiratory support): the use of nasal cannula and facemask to inhale oxygen with no requirement of intubation during the hospital stay.

Statistical analysis

Continuous variables are expressed as medians and interquartile ranges (IQRs). Categorical variables are summarized as counts (n) and percentages (%). Missing data were not imputed. We used Kruskal-Wallis rank test and Fisher's exact test to compare the corresponding results among non-invasive respiratory support and early and late intubation groups. Given the incidences of all outcomes investigated exceeding 15% in which odds ratio would overstate the risk ratio, perhaps dramatically, the log-binomial regression models were used to yield risk ratios of the risk factors for intubation, late intubation and in-hospital death [22]. The risk ratios (RRs) were reported if applicable. The Kaplan-Meier statistic and the survival curves were used to estimate the risk of mortality among comparisons. A two-stage procedure was performed for comparing hazard ratios among three groups. Due to the explorative nature of the study, no formal hypotheses were implemented to drive the sample size calculation, and we included the maximum number of patients who met the inclusion criteria. *P* values less than 0.05 were considered significant except for 0.0125 for two-stage procedure statistics. All analyses were performed in SPSS (version 25, IBM Corp, Armonk, NY, USA) and Stata (version 16; Stata Corp, College Station, TX, USA).

Results

Characteristics and clinical outcomes of patients with COVID-19-related ARDS

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. Of these, 70 patients developed ARDS. We included 65 of these cases with laboratory confirmation and excluded five cases. The details of enrolment are provided in Fig. 1.

The median age of the 65 included ARDS patients was 67.0 years (IQR, 56.0–78.0), with the 53.8% over 65 years and the 70.8% males (Table 1). The median body mass index (BMI) was 24.4 kg/m² (IQR, 22.4–26.7). More than two-thirds of patients (n = 44) had at least three symptoms. The most three self-reported symptoms were fever (84.6%), cough (70.8%), and shortness of breath (43.1%). Vital signs evaluated at hospital admission revealed fever in 23 patients (35.4%) and median 20.0 breaths per minute (IQR, 20.0–25.0). Forty-four patients had at least one comorbidity. More than two-thirds of the patients (n = 45) were graded as severe pneumonia by physicians. From the symptom onset to hospital admission the median number of days was 8.0 (IQR, 5.0–10.0), from hospital admission to ARDS diagnosis it was only 1.0 (IQR, 0.0–4.0), from symptom onset to ARDS diagnosis it was 11.0 (IQR, 8.0–13.0). All patients demonstrated bilateral pulmonary infiltrates. The median oxygenation index (OI) at ARDS diagnosis was 184.5 (IQR, 134.0–230.0) and 47.7% of all patients had moderate ARDS at the beginning (OI between 199 and 100) (Table 1). Most patients received antiviral and empiric antibiotic therapies. The 78.5% of the patients took methylprednisolone (glucocorticoid) and 24.6% took vasopressors. Nearly half required ICU-level care, eight adopted prone position ventilation, and six and four received CRRT and ECMO respectively, to sustain life. The median ICU and hospital stays were 15.0 days (IQR, 10.0–20.0) and 21.0 days (IQR, 12.0–34.0). Twenty-four deaths (38.1%) occurred, and the main cause was acute respiratory condition (62.5%). For mild, moderate, and severe ARDS, the mortality rates were 20.0%, 41.9% and 85.7% respectively.

Laboratory indices tested at admission (Table 2) suggested that most patients had systemic hyperinflammation, indicated by the increased erythrocyte sedimentation rate (ESR), C-reactive protein level and procalcitonin level. Quite a few patients demonstrated reduced albumin/globulin ratio and increased total bilirubin and aspartate transaminase levels, suggesting liver injury, and elevated lactate dehydrogenase and cardiac troponin I levels, indicating heart injury. Approximately four-fifths of the patients had lymphocytopenia. Some patients were suspected of having pancreatic injury indicated by the high blood glucose level, and kidney injury based on the elevated serum creatinine level and reduced glomerular filtration rate (GFR). Next, a high international normalized ratio, prolonged prothrombin time and elevated D-dimer level were reported in several patients. Some patients demonstrated leukocytosis, neutrophilia, thrombocytopenia and reduced hemoglobin concentrations.

Comparisons among patients with non-invasive respiratory supports, early, and late intubation

Compared with the late-intubation group, patients with early intubation had significantly shorter time from symptom onset to intubation ($P = 0.023$), from hospital admission to intubation ($P = 0.011$), and from ARDS diagnosis to intubation ($P < 0.001$) (Fig. 2A). We observed the differences on OI values ($P = 0.015$) at ARDS diagnosis and proportions of ARDS classifications ($P = 0.052$) among no-intubation, early-intubation, and late-intubation groups. Patients with early intubation presented the lowest OI ratios (median, 133.9; IQR 98.3-183.2) and the highest proportion of moderate and severe ARDS (90%). But patients with late intubation had a slightly higher OI ratios (median, 159.0; IQR 134.0-203.0) compared to early-intubation group. Consequently, these late intubation patients received the most aggressive therapies including glucocorticoids (100.0%), vasopressors (50.0%), CRRT (50.0%), prone position ventilation (50.0%), ECMO (50.0%), and ICU-level care (80.0%) in the context of the associated differences occurring among the three groups ($P = 0.016$, $P = 0.007$, $P < 0.001$, $P = 0.001$, $P < 0.001$, $P < 0.001$). The mortality rate at discharge in the late-intubation group was 90.0% compared with 50.0% in the early-intubation group and 23.3% in the no-intubation group ($P < 0.001$, Table 3, Fig. 2B). The hospital survival probability of the late-intubation group was the lowest among the three groups (Fig. 2C).

Risk factors associated with intubation and hospital death

As summarized in Table 4, patients aged equal and older than 65 years (RR, 2.56; 95% CI 1.06-6.18, $P = 0.037$), had fatigue (RR, 2.63; 95% CI 1.30-5.31, $P = 0.007$), hypertension (RR, 2.05; 95% CI 1.03-4.08, $P = 0.042$), GFR < 80 ml/min/1.73m² (RR, 2.13; 95% CI 1.02-4.48, $P = 0.045$) at admission, lower OI ratio (higher values RR, 0.99; 95% CI 0.99-0.99, $P = 0.000$), or OI ratio less than 150 (RR, 2.61; 95% CI 1.25-5.43, $P = 0.010$) at ARDS diagnosis were more likely to have the intubation.

Regarding hospital death, the ARDS patients on the intubation had 3.01 RR (95% CI, 1.63-5.62, $P = 0.000$), and the patients receiving the late intubation had 3.18 RR (95% CI, 1.98-5.12, $P = 0.000$). ARDS patients who were older (RR, 2.56; 95% CI 1.06-6.18, $P = 0.037$), aged equal and over 65 years (RR, 2.56; 95% CI 1.06-6.18, $P = 0.037$), had fatigue (RR, 2.56; 95% CI, 1.01-6.08, $P = 0.047$) were more likely to die in hospital. Patients demonstrating lower OI ratio (higher values RR, 0.99; 95% CI, 0.99-1.00, $P < 0.001$), OI ratios lower than 200 (RR, 2.50; 95% CI, 1.07-5.83, $P = 0.034$), 150 (RR, 2.43; 95% CI, 1.30-4.57, $P = 0.006$) or 100 (RR, 2.67; 95% CI, 1.64-4.34, $P < 0.001$) were associated with hospital death.

Discussion

In this study, we found that the ARDS caused by COVID-19 was not the typical ARDS defined by the Berlin criteria [20] due to longer onset time, multiple organs injuries and higher mortality in moderate and severe form. The late intubation group, but not the early intubation group, with less severity at admission,

needed more aggressive therapies and cares, and was highly associated with in-hospital death. The predictors for intubation were not same as those for death.

The study complements the existing studies on COVID-19-related ARDS and enriches the understanding of its clinical features. The median onset time for COVID-19-related ARDS was 11.0 days (IQR, 8.0–13.0), which is inconsistent with the 1-week onset limit reported for ARDS caused by other factors [20]. The findings should alert physicians to pay more attention to the development of ARDS in COVID-19 patients with a disease course of more than a week for timely treatment. The mortality rates of moderate and severe COVID-19-related ARDS were 41.9% and 85.7% in our study, which are much higher than 32% and 45% as reported in typical ARDS [23]. One possible explanation is silent hypoxemia as proposed by several experts, that clinical symptoms are inconsistent with the severities of hypoxemia which would result in delay treatment [6, 24]. From the perspective of therapy, a more suitable classification of ARDS severity that can accurately identify patients requiring a timing therapy for COVID-19 has been proposed [5].

The majority of patients with ARDS in this study were men over 65 years old with hypertension and/or diabetes but not overweight. A large proportion of the patients had palpitations and chest distress at admission and later demonstrated injuries in the heart, liver, kidney, and pancreas during hospitalization. This finding is consistent with the previous findings that the new coronavirus can attack the tissues of other organs in addition to the respiratory tract [25-28]. Fundamental experiments revealed the mechanism that SARS-CoV-2 can enter the circulation by infecting the endothelium of lung tissue; the virus then directly attacks the other organs or triggers a systematic hyperinflammation response, resulting in secondary attacks to the organs [29].

We noticed that apart from antiviral therapy, many other antibiotics were administered to combat bacterial co-infections, and some patients received glucocorticoids to alleviate hyperinflammation indicated by the increasing levels of ESR, C-reactive protein and procalcitonin. We observed that patients with COVID-19-related ARDS presented with severe lymphocytopenia on admission, required aggressive therapies such as CRRT and ECMO, needed long hospital stays (median, 21.0 (IRQ, 12.0–34.0) days), but died more in hospital. All in all, updating the management strategy is highly suggested, including monitor longer to the development of COVID-19-related ARDS and re-categorize the atypical ARDS to give timing therapies.

Another important finding was that the groups of early and late intubations and the early intubation was not associated with in-hospital death. By contrast, the late-intubation group required more advanced therapies, presented a higher RR for death and trended the lowest hospital survival probabilities among the three groups. The conclusion is consistent with one study that each additional day between hospital admission and intubation was significantly associated with higher in-hospital death [15]. Because most of patients died of acute respiratory failure, the explanation coming forth that cannot be excluded was the delayed intubation. In our cohort, we noticed patients intubated late were not sicker at admission than those intubated early and their median OI ratios at ARDS diagnosis were slightly above the threshold of

150, where the intubation census usually suggests perform invasive mechanical ventilation if OI below 150 [16]. Given that the COVID-19-caused ARDS could present silent hypoxemia [6], where the degrees of dyspnea are inconsistent with the severities of hypoxemia, that would result in delayed intubation once sudden decompensation occurs. Many years ago, Shoemaker et al. [30] reported there is a close association between the oxygen debt accumulated over 48 hour and the chance of survival in critical patients. We noticed that even early intubation group had 50% in-hospital mortality in the cohort, as similar as the overall global data calculated recently by the systematic review [13]. Our current ventilatory approach or intubation criteria is to delay intubation if it clinically appears safe and feasible [18]. However, the findings of the cohort may suggest proactive intubation instead of salvage means for critical illness of COVID-19. This is supported by some accurate observations that many of COVID-19 patients deteriorated precipitously and that they may be more safely intubated at an earlier stage [6, 7]. Additionally, a high work of breathing generating large swings in intrapleural pressure may result in self-inflicted lung injury and worsen the disease [7], as certainly a rationale for early intubation. However, the exact definition of the early intubation for COVID-19 critical illness is challenging. To intubate the patients early before sudden decompensation occurs while avoiding the risk of iatrogenic injury should be considered simultaneously in the face of so much high mortality.

The predictors for intubation and death were not same. The cohort found that the COVID-19 ARDS patients who had hypertension or GFR < 80 ml/min/1.73m² were more likely to have the intubation but not death. This may suggest different development mechanism between death and intubation for COVID-19 ARDS patients.

We found lower OI ratio and OI less than 150 were associated with intubation and death. OI ratio less than 200 or 100 was associated with just death. Lower OI ratios mean acute respiratory failure and OI less than 150 already indicates extreme respiratory failure [31]. The OI predictors for intubation or death reflecting the severity of acute lung injury as well were not reported in any study [31-34]. Our findings on OI ratio predictors shall support the strategy that “patients with a OI ratio less than 300 mmHg should be prepared for intubation if there are indications, such as poor oxygenation after 2 hours of high-flow oxygen therapy or non-invasive ventilation, and OI less than 150” [16]. That requires early recognition and timing treatment of patients with worsening respiratory function during COVID-19 treatment. Additionally, we also found older ages could predict the death in COVID-19-related ARDS patients. The older age was therefore verified as the risk factor for death of critical patients as it for general COVID-19 patients [33]. The limited hospital resources and treatment strategy therefore shall focus on the elder age to reduce the death numbers from critical illness of COVID-19.

The strengths of the study are as follows: the study cohort included patients from two hospitals in two cities of Hubei province, which increases the generalisability of the findings; phenotyping of clinical characteristics was performed based on respiratory support strategies and IMV-associated groups, defined as early and late intubation according to 1-week cut-off point; reported adjustment RRs instead of crude RRs. However, the study has some limitations. First, it is a retrospective cohort conducted at two hospitals. As is known, it was hard to perform a perspective cohort when epidemic happened and

developed everywhere. As we have sparse new COVID-19 cases now, we hope our new findings can encourage a larger cohort study or even randomly controlled trials in other regions who are experiencing the outbreak and in the urgent need to adjust the strategy. Second, the information such as respiratory function variables during the treatment course at the early and late intubations should be collected and analysed. The current cohort's findings propose the need to further explore the better timing of intubation for reducing mortality.

Conclusions

We found that the SARS-CoV-2-caused ARDS was not typical ARDS for which the management strategies should be adjusted accordingly. We studied the early- and late-intubation groups, based on 1-week cutting point, which had significant differences in the days from symptoms onset/hospital admission/ARDS diagnosis to intubation. Compared with the early intubation, the late intubation presenting less severity at admission but required more advanced treatment and had the higher risk of death. Predictors of the intubation were not same as those of in-hospital death. The findings had implications in modulating the management strategy for ARDS of COVID-19, and in supporting the early intubation strategy.

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

This manuscript adheres to the applicable CONSORT guidelines. 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 and given the context of ongoing infectious diseases.

Consent for publication

Not applicable

Availability of data and materials

After publication, the data will be made available to others on reasonable requests to the corresponding author. A proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests. Additional materials might also be required during the process of evaluation. Deidentified participant data will be provided after approval from the corresponding author and Wuhan and Hong Hu Hospitals.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JLM: This author helped with study design, data collection, write the manuscript and edit for critical content.

MZQ: This author helped with data collection and edit for critical content.

HMS: This author helped with data collection and edit for critical content.

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Tables

Table 1. Demographics, characteristics, and outcomes of COVID-19 patients developing ARDS

Study variables	Value, no./total no. (%) or median (IQR)
No. of patients	65
Age	
median, IQR	67.0 (56.0-78.0)
≥ 65 years	35/65 (53.8%)
Male sex	46/65 (70.8%)
BMI*	
median, IQR	24.4 (22.4-26.7)
≥ 25	20/65 (30.8%)
Smoke history	7/65 (10.8%)
Alcohol used	9/65 (13.8%)
Days from symptoms onset to hospital admission (median, IQR)	8.0 (5.0-10.0)
Initial symptoms	
Fever	55/65 (84.6%)
Cough	46/65 (70.8%)
Short of breath	28/65 (43.1%)
Fatigue	20/65 (30.8%)
Expectoration	17/65 (26.2%)
Palpitation and chest distress	17/65 (26.2%)
Number of complaints ≥ 3	44/65 (67.7%)
Vital signs on admission	
Fever on admission (≥ 37.2°C)	23/65 (35.4%)
Breath rate (median, IQR)	20.0 (20.0-25.0)
Heart rate (median, IQR)	90.0 (79.0-98.0)
SBP (median, IQR)	132.0 (122.0-142.0)
DBP (median, IQR)	78.0 (71.0-88.0)
MAP (median, IQR)	96.7 (89.0-105.0)
Severity of pneumonia graded by physicians	

Mild	2/65 (3.1%)
Severe	18/65 (27.7%)
Critical	45/65 (69.2%)
Comorbidities	
Hypertension	20/65 (30.8%)
Diabetes	10/65 (15.4%)
Cardiovascular disease	8/65 (12.3%)
Brain disease	6/65 (9.2%)
Chronic lung disease	2/65 (3.1%)
Number of coexisting disorders ≥ 1	44/65 (67.7%)
Days from hospital admission to ARDS diagnosis (median, IQR)	1.0 (0.0-4.0)
Days from symptoms onset to ARDS diagnosis (median, IQR)	11.0 (8.0-13.0)
Chest imaging, bilateral infiltrate	65/65 (100%)
Oxygenation Index on ARDS Diagnosis	
median (IQR)	184.5 (134.0-230.0)
300-200	27/65 (41.5%)
199-100	31/65 (47.7%)
<100	7/65 (10.8%)
Treatments	
Antiviral therapy	63/65 (96.9%)
Intravenous antibiotic	60/65 (92.3%)
Glucocorticoid (methylprednisolone)	51/65 (78.5%)
Vasopressor	16/65 (24.6%)
Admission to ICU	29/65 (44.6%)
Prone positioning	8/65 (12.3%)
Continuous renal-replacement therapy	6/65 (9.2%)
ECMO	4/65 (6.2%)
Outcomes	

Failure of noninvasive respiratory support*	20/65 (31.7%)
Median ICU stay (day, IQR) †	15.0 (10.0-20.0)
Median Hospital stay (day, IQR)	21.0 (12.0-34.0)
Death in hospital	24/65 (36.9%)
Death in OI \geq 200	5/25 (20.0%)
Death in 200 > OI \geq 100	13/31 (41.9%)
Death in OI < 100	6/7 (85.7%)
Death due to acute respiratory failure	15/24 (62.5%)

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

† Data summarized from 29 patients admitted into ICU.

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

Table 2. Initial laboratory indices of COVID-19 patients developing ARDS

Laboratory indices on admission	Reference values	Value, median (IQR)	No. of patients with value deviation from reference (%)
Hematologic			
Lymphocyte count /mm ³	1000-4800	670 (430-1040)	47/65 (72.3%) ^b
WBC count /mm ³	4000-10000	7340 (4700-10700)	19/65 (29.2%) ^a
Neutrophil count /mm ³	2500-8000	6320 (3440-9150)	21/65 (32.3%) ^a
Platelet count /mm ³	150-450	199 (146-236)	16/65 (24.6%) ^b
Hemoglobin, g/dL	12-17.5	13.1 (11.6-14.0)	20/65 (30.8%) ^b
Biochemical			
TBIL, μmol/L	3.4-17.1	13.0 (10.1-18.3)	48/65 (73.8%) ^a
AST, U/L	10-40	39.0 (25.0-50.0)	27/65 (41.5%) ^a
ALT, U/L	7-56	27.0 (20.0-35.0)	5/65 (7.7%) ^a
Total protein, g/L	60-83	64.0 (60.7-68.3)	15/65 (23.1%) ^b
Albumin, g/L	32-45	34.1 (31.2-37.5)	20/65 (30.8%) ^b
Albumin/Globulin	1.5-2.5	1.13 (0.95-1.39)	55/65 (84.6%) ^b
LDH, unit/L	140-280	371.5 (227.0-519.0)	40/65 (61.5%) ^a
cTnl, ng/mL	0-0.04	0.02 (0.01-0.04)	15/65 (23.1%) ^a
Glucose, mmol/L	3.9-7.1	7.9 (6.0-10.5)	37/65 (56.9%) ^a
Creatinine, μmol/L	57-110	74.2 (59.0-93.0)	12/65 (18.5%) ^a
GFR, ml/min/1.73m ²	80-125	89.0 (62.0-104.0)	27/65 (41.5%) ^b
Potassium, mmol/L*	3.5-5.0	3.9 (3.7-4.3)	11/59 (18.6%) ^b
Sodium, mmol/L*	135-145	137.8 (134.8-139.3)	15/59 (25.4%) ^b

D-Dimer, mg/L	0.0-0.5	0.6 (0.2-2.4)	34/65 (52.3%) ^a
PT, s	10.5-13.5	13.1 (11.9-14.7)	27/65 (41.5%) ^a
INR	≤1.1	1.1 (1.1-1.2)	38/65 (58.5%) ^a
Inflammation related			
ESR, mm/ht	0-20	62.5 (31.0-81.0)	52/58 (89.7%) ^a
C-Reactive Protein, mg/L	5-10	59.1 (20.1-108.6)	57/65 (87.7%) ^a
Procalcitonin, µg/L	≤0.10	0.12 (0.05-0.38)	35/65 (53.8%) ^a

a. Above the reference limit

b. Below the reference limit

* Data regarding the Potassium and Sodium were missing for 6 patients respectively (9.2%).

† Data regarding the ESR were missing for 7 patients (10.8%).

Abbreviations: 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.

Table 3. Consequences among noninvasive respiratory support and early and late intubation groups in COVID-19-related ARDS patients

Oxygenation Index on ARDS Diagnosis, median (IQR)	200.0 (158.0-247.5)	133.9 (98.3-183.2)	159.0 (134.0-203.0)	0.015
300-200	23/45 (51.1%)	1/10 (10.0%)	3/10 (30.0%)	
199-100	19/45 (42.2%)	6/10 (60.0%)	6/10 (60.0%)	
<100	3/45 (6.7%)	3/10 (30.0%)	1/10 (10.0%)	0.052
Systemic glucocorticoids	31/45 (68.9%)	10/10 (100%)	10/10 (100%)	0.016
Vasopressor	6/45 (13.3%)	5/10 (50.0%)	5/10 (50.0%)	0.007
Use of continuous renal-replacement therapy	0/45 (0.0%)	1/10 (10.0%)	5/10 (50.0%)	0.000
Prone positioning	0/45 (0.0%)	3/10 (30.0%)	5/10 (50.0%)	0.000
ECMO	0/45 (0.0%)	1/10 (10.0%)	5/10 (50.0%)	0.000
Admission to ICU	14/45 (31.1%)	7/10 (70.0%)	8/10 (80.0%)	0.005
Death in the hospital	10/45 (23.3%)	5/10 (50.0%)	9/10 (90.0%)	0.000

* Respiratory support strategies include nasal cannula inhalation, high-flow nasal cannula therapy, and noninvasive ventilation.

† Patients of hospital admission temperature ≥ 37.2 °C.

‡ Fisher's exact test used for analysing percentage data.

Abbreviations: SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: Mean Arterial Pressure, GRF: glomerular filtration rate ECMO: Extracorporeal membrane oxygenation; NA: not applicable.

Table 4. Log-binominal regression of factors associated with intubation and death

Variables	Intubation (n=20)		Death (n=24)	
	RR*	P value	RR*	P value
Intubation Ventilation				
Intubation	NA	NA	3.01 (1.63-5.62)	0.000
Early intubation	NA	NA	1.39 (0.68-2.86)	0.363
Late Intubation	NA	NA	3.18 (1.98-5.12)	0.000
Factors				
Age, years	1.02 (0.99-1.04)	0.159	1.04 (1.02-1.05)	0.000
Age ≥ 65 years	2.56 (1.06-6.18)	0.037	3.24 (1.38-7.59)	0.007
Fatigue complaint	2.63 (1.30-5.31)	0.007	2.15 (1.18-3.91)	0.012
Hypertension	2.05 (1.03-4.08)	0.042	1.25 (0.65-2.39)	0.501
GFR < 80 ml/min/1.73m ²	2.13 (1.02-4.48)	0.045	1.20 (0.64-2.25)	0.561
Oxygenation Index				
Values	0.99 (0.99- 0.99)	0.000	0.99 (0.99-1.00)	0.000
<200	2.63 (1.00-6.96)	0.051	2.50 (1.07-5.83)	0.034
<150	2.61 (1.25-5.43)	0.010	2.43 (1.30-4.57)	0.006
<100	2.00 (0.93-4.29)	0.075	2.67 (1.64-4.34)	0.000

*All RRs adjusted for Age ≥ 65 years, except for age and Age ≥ 65 years adjusted for Oxygenation Index.

† Robust Poisson regression substituting for binomial regression due to fail in converge. Abbreviations: RR; risk ratio; GFR: glomerular filtration rate

Figures

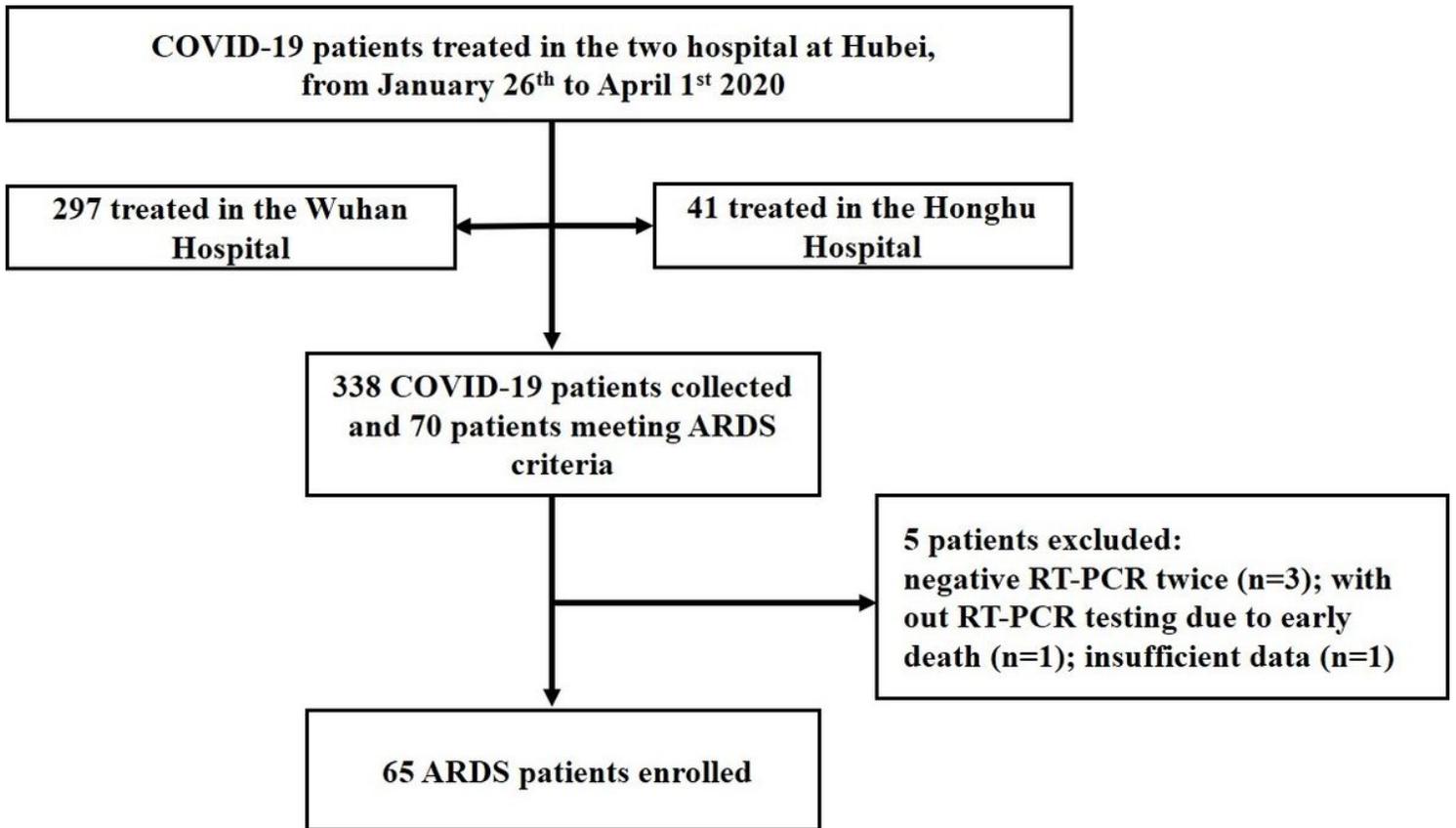
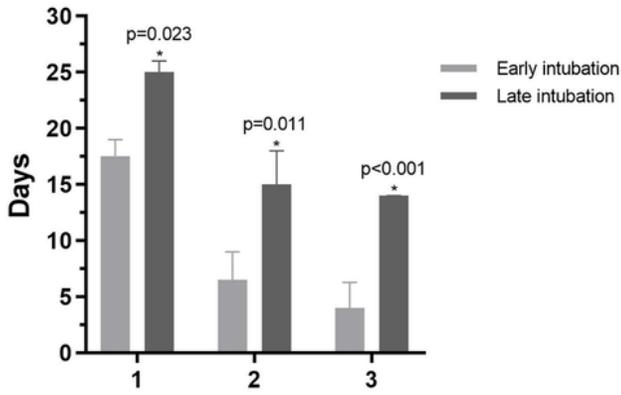


Figure 1

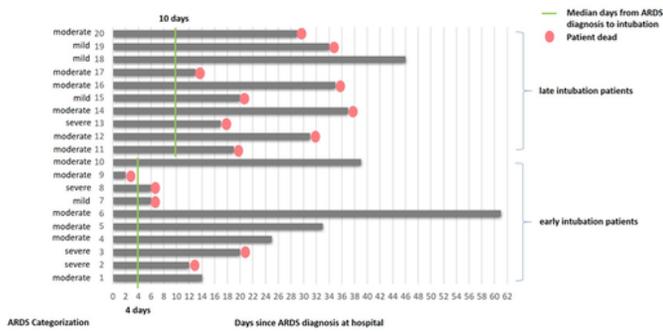
Enrolment of COVID-19-related ARDS patients at Wuhan and Honghu hospitals

A



Median (IQR) days from onset of symptoms to (1) hospital admission, (2) ARDS diagnosis, and (3) intubation

B



ARDS Categorization

C

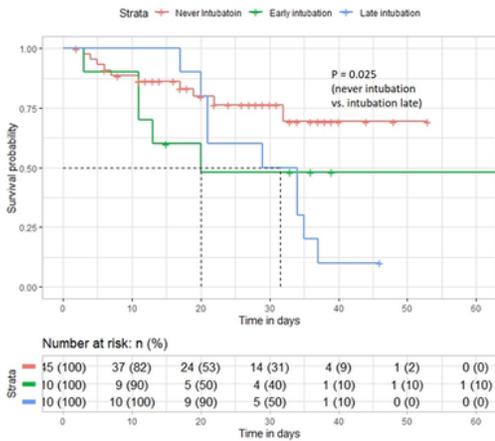


Figure 2

Information for intubation group classifications and the outcomes. A. Median (IQR) days from onset of symptoms to hospital admission, ARDS diagnosis, and intubation; B. 20 deaths and their intubation time; C. Hospital survival probability of never-, early-, and late-intubation groups. * A statistical difference based on $P < 0.05$.