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Original Article

Clinical characteristics and prognosis of COVID-19 patients with tracheal intubation

Yingtao Lian[1*], Guo Hou[2*], Wenjie Xie[2], Zhentong Zhong[2], Kesheng Huang[2], Guang Li[2], Lan Yao[2], Lizhi Feng[2], Zhui Yu[2]

[1]*Department of Anesthesiology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, P. R. China;* [2]*Department of Critical Care Medicine, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, P. R. China.*
[*]*Co-first authors.*

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Abstract: This study aimed to describe the clinical characteristics and prognosis of COVID-19 patients who received tracheal intubation and mechanical ventilation. A total of 52 critical COVID-19 patients who received tracheal intubation were retrospectively included. The primary data including clinical features, laboratory results, and the outcomes were collected and analyzed. Among the 52 patients who received tracheal intubation, 14 were successfully extubated within two weeks and 38 failed extubation. The patients in the extubation failure group were significantly older than the patients in the successful extubation group (median age, 67.50 years vs 55.50 years). The median values of SpO_2 and the PaO_2/FiO_2 (P/F) before tracheal intubation were significantly lower in extubation failure group than the those in successful extubation group (SpO_2: 78.50% vs 85%, P/F: 71.50 mmHg vs 84.50 mmHg). Compared with the successful extubation group, the extubation failure group was found to have a significantly lower 28-day survival rate (21.05% vs 100%). Patients with extubation failure had more severe multi-organ injuries. Besides, a more severe hypoxia level was found to be associated with the failure of extubation and subsequent poor prognosis. Therefore, tracheal intubation and timely invasive mechanical ventilation should be administered in COVID-19 patients with refractory hypoxemia.

Keywords: COVID-19, SARS-CoV-2, 2019-nCoV, epidemiology, tracheal intubation, invasive mechanical ventilation

Introduction

Since late December 2019, a series of cases of viral pneumonia with unknown etiology were reported in Wuhan, Hubei Province, China [1-3]. The causative pathogen was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4], and the disease caused by SARS-CoV-2 was named coronavirus disease 2019 (COVID-19) by the WHO. Presently, COVID-19 is causing several outbreaks in different parts of the world. SARS-CoV-2 causes damage to several organs of the body [5, 6]. Among these organs, lungs are primarily affected by this virus, and acute lung injury/acute respiratory distress syndrome (ARDS) is the main manifestation. Acute lung injury/ARDS eventually leads to refractory hypoxemia that causes death if patients do not receive effective oxygen therapy. We observed that multiple organ dysfunction syndromes usually occurred secondary to refractory hypoxemia. It seems that lung injury/ARDS is the driving force of other organ damages and dysfunctions. The patients suffering from acute life-threatening hypoxemia during the clinical course may require ventilatory support [7]. If hypoxemia is not treated in time, the patient's condition will rapidly deteriorate because of associated disorders including acute kidney injury, coagulation dysfunction, heart failure, shock, and mental disorders. Studies suggested that approximately 45% of the critically ill COVID-19 patients in the intensive care unit (ICU) required tracheal intubation and invasive mechanical ventilation (IMV) [3, 8]. Although the ventilator weaning rate varied between different ICUs, tracheal intubation and IMV are still important components of therapies for respiratory failure including refractory hypoxemia in severe and critical COVID-19 patients [9].

Previous studies helped us to understand the biology of SARS-CoV-2 and unravel the clinical course, disease outcomes, and new diagnostic for COVID-19 [1, 10, 11]. Many researchers are now exploring the effects of various antiviral drugs, vaccines, convalescent plasma, acute kidney injury and continuous renal replacement therapy, myocardial damage, inflammatory storm and plasma purification, and so on. However, the appropriate timing of tracheal intubation and IMV during the clinical course of SARS-CoV-2 induced ARDS remains to be elucidated. Therefore, this study aimed at investigating the effect of early and late tracheal intubation on outcomes of critical COVID-19 patients through the analysis of their clinical characteristics.

Methods

Study design and cases

This single-center, retrospective, observational study was carried out at Renmin Hospital of Wuhan University, which is one of the major tertiary teaching and government authorized hospitals for patients with COVID-19. All enrolled patients were confirmed of COVID-19 as per the WHO interim guidance [12] and National Health Commission of China, and were admitted to Renmin Hospital of Wuhan University between January 1, 2020, and April 3, 2020. COVID-19 was diagnosed by the nucleic acid test with high-throughput sequencing or real-time reverse transcriptase-polymerase chain reaction (RT-PCR) [2]. Further, the CT scan was used to confirm viral pneumonia [13, 14]. Critical COVID-19 patients with tracheal intubation were identified based on admission logs and patients, medical history. All included patients were divided into two groups: successful extubation group (patients extubated within two weeks and no further intubation and invasive mechanical ventilation for seven consecutive days) and extubation failure group (patients with extubation failure within two weeks and tracheotomy, or extracorporeal membrane oxygenation [ECMO], or death).

This study was approved by the Ethics Committee of the Renmin Hospital of Wuhan University (WDRY2020-K026).

Data collection

The clinical data of the patients were collected from electronic medical records that included epidemiological, clinical, laboratory, radiological, treatment, and outcomes data. The data were reviewed by a trained team of physicians.

We classified the data based on the patient, s age, sex, comorbidities (hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic liver disease), signs and symptoms (fever, cough, myalgia, dyspnea, headache), vital signs at the time of admission (heart rate, mean arterial pressure [MAP], respiratory rate, saturation of pulse oxygen [SpO_2]), vital signs and laboratory findings before tracheal intubation (heart rate, MAP, respiratory rate, SpO_2, arterial blood gas analysis, oxygen therapy, complete blood count, etc.), and living status. The clinical outcomes (discharge, or in-hospital mortality) were monitored up to April 30, 2020, the final day of follow-up.

Statistical analysis

The statistical analyses were performed using SPSS version 20.0 (IBM, Illinois, USA). Categorical variables were described as frequency rates and percentages, and continuous variables were expressed using mean ± standard deviation, or median, and inter quartile range (IQR) as appropriate. Continuous variables were compared using independent samples t-tests when the data were normally distributed; otherwise, the Mann-Whitney test was used. Proportions for categorical variables were compared using the χ^2 test. When the sample was limited, the Fisher exact test was used. Kaplan-Meier methods were used to do the survival analyses. A *p*-value of less than 0.05 was considered statistically significant.

Results

By April 3, 2020, 1248 patients were admitted to Renmin Hospital of Wuhan University with confirmed COVID-19. Out of the admitted 1248 patients, 1196 patients who were not administered tracheal intubation and invasive ventilation were excluded. Only 52 critical COVID-19 patients who were treated with tracheal intubation and invasive ventilation were included in our study. Out of the 52 patients, 14 were successfully extubated within two weeks, 38 either failed extubation in two weeks and received tracheotomy or ECMO, or died before the last day of follow up (**Figure 1**).

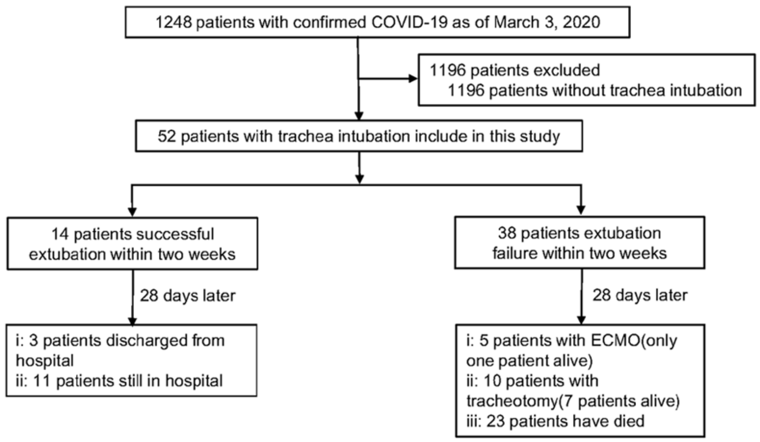

Figure 1. Study flow diagram. COVID-19 = coronavirus disease 2019, ECMO = extracorporeal membrane oxygenation.

Baseline characteristics

This retrospective study included 52 eligible patients (median age, 63.50 years and IQR, 52.25-70.75) with COVID-19, of which 32 (61.54%) were males and 20 (38.46%) were females. Of the 52 patients, 18 patients were found to have no comorbidities and 34 patients were found to have at least one comorbidity: hypertension (26: 50.00%), diabetes (7: 13.46%), cardiovascular disease (9: 17.31%), chronic respiratory disease (3: 5.77%) and chronic liver disease (2: 3.85%). Signs and symptoms of the patients during the time of admission to the hospital included fever (48: 92.31%), cough (24: 46.15%), myalgia (14: 26.92%), dyspnea (9: 17.31%), and headache (4: 7.69%). Median time from onset of symptoms to admission to the hospital was 10.00 days (IQR, 7.00-12.00). The median values of heart rate, MAP, respiratory rate, and SpO_2 were 89.00 bpm (IQR, 82.00-103.75), 99.00 mmHg (IQR, 92.25-105.75), 23.00 times/minute (IQR, 20.00-30.00), and 93.00% (IQR, 90.00-95.75), respectively (**Table 1**).

Basic characteristics were compared between the patients of successful extubation group and extubation failure group. Older patients (median age, 67.50 years vs 55.50 years, P = 0.017) were associated with significantly worse outcome of offline failure. Differences in other indicators such as sex, comorbidities, signs and symptoms, heart rate, MAP, respiratory rate, SpO_2, and time elapsed from onset of symptoms to admission to the hospital were statistically insignificant.

Differences in laboratory findings before tracheal intubation

The differences in laboratory findings before tracheal intubation between successful extubation group and extubation failure group are described in **Table 2**. The median levels of creatine kinase-MB (CK-MB) and hypersensitive troponin I were significantly higher in extubation failure group (CK-MB: 2.59 ng/mL, P = 0.006; hypersensitive troponin I: 0.13 ng/mL, P = 0.005) as compared with the corresponding levels in successful extubation group (CK-MB: 1.29 ng/mL, hypersensitive troponin I: 0.02 ng/mL). Similarly, the median D-dimer and fibrin degradation products (FDP) levels were significantly higher in extubation failure group (D-dimer: 20.25 mg/L, P = 0.025; FDP: 79.49 mg/L, P = 0.021) as compared with successful extubation group (D-dimer: 11.76 mg/L, FDP: 34.14 mg/L). The median levels of platelet count was significantly higher in successful extubation group (0.82×10^9/L, P = 0.003) as compared with the corresponding levels in extubation failure group (0.56×10^9/L). However, the differences in hematological and biochemical parameters such as white blood cell count, lymphocyte count, haemoglobin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, serum creatinine, prothrombin time and activated partial thromboplastin time between the two groups were not statistically significant.

Comparison of vital signs and blood gas analysis

We compared the vital signs and blood gases of the patients of successful extubation group and extubation failure group before tracheal intubation (**Table 3**). Median SpO_2 and median PaO_2/FiO_2 (P/F) before tracheal intubation were significantly lower in extubation failure group (SpO_2: 78.50%, P = 0.033; P/F: 71.50 mmHg, P = 0.040) as compared with those of successful extubation group (SpO_2: 85.00%, P/F: 84.50 mmHg). Moreover, no significant differences were observed in heart rate, MAP, respiratory rate, PH, PaO_2, $PaCO_2$, lactate, and

Table 1. Demographics and baseline characteristics of patients with COVID-19

	All patients (n = 52)	Successful extubation (n = 14)	Extubation failure (n = 38)	*p* Value
Age, y	63.50 (52.25-70.75)	55.50 (51.50-62.75)	67.50 (55.25-73.00)	0.017
Sex				
Female	20 (38.46)	6 (42.86)	14 (36.84)	0.693
Male	32 (61.54)	8 (57.14)	24 (63.16)	
Comorbidities				
Hypertension	26 (50.00)	7 (50.00)	19 (50.00)	>0.99
Diabetes	7 (13.46)	2 (14.29)	5 (13.16)	>0.99
Cardiovascular disease	9 (17.31)	2 (14.29)	7 (18.42)	>0.99
Chronic respiratory disease	3 (5.77)	0	3 (7.89)	0.555
Chronic liver disease	2 (3.85)	1 (7.14)	2 (5.26)	>0.99
None	18 (34.62)	5 (35.71)	13 (34.21)	0.919
Signs and symptoms				
Fever	48 (92.31)	13 (92.86)	35 (92.11)	>0.99
Cough	24 (46.15)	7 (50.00)	17 (44.74)	0.736
Myalgia	14 (26.92)	4 (28.57)	10 (26.32)	>0.99
Dyspnea	9 (17.31)	3 (21.43)	6 (15.79)	0.688
Headache	4 (7.69)	1 (7.14)	3 (7.89)	>0.99
Onset of symptom to admission to the hospital, d	10.00 (7.00-12.00)	9.00 (5.75-12.25)	10.00 (7.00-12.00)	0.407
Heart rate, bpm	89.00 (82.00-103.75)	84.50 (81.25-103.00)	89.00 (81.50-105.25)	0.820
MAP, mmHg	99.00 (92.25-105.75)	96.50 (90.00-101.50)	100.00 (92.75-107.25)	0.397
Respiratory rate	23.00 (20.00-30.00)	27.50 (22.25-30.75)	22.00 (19.00-29.25)	0.097
SpO_2, %	93.00 (90.00-95.75)	92.00 (89.50-94.25)	93.50 (90.00-96.00)	0.443

Data are median (IQR) or n (%). COVID-19 = novel coronavirus disease 2019. MAP = mean arterial pressure. SpO_2 = saturation of pulse oxygen.

Table 2. Differences in laboratory findings before tracheal intubation between successful intubation and extubation failure patients with COVID-19

	Normal Range	Successful intubation (n = 14)	Extubation failure (n = 38)	*P* Value
White blood cell count, $\times 10^9$/L	3.5-9.5	13.38 (11.74-17.45)	15.43 (10.17-19.46)	0.757
Lymphocyte count, $\times 10^9$/L	1.1-3.2	0.82 (0.55-1.15)	0.56 (0.39-0.92)	0.108
Platelet count, $\times 10^9$/L	125-350	219.00 (181.00-257.25)	137.50 (97.00-223.00)	0.003
Haemoglobin concentration, g/L	130-175	122.00 (110.75-129.00)	123.50 (112.75-133.25)	0.613
Alanine aminotransferase, U/L	9-50	34.00 (23.00-50.75)	25.50 (16.00-60.25)	0.522
Aspartate aminotransferase, U/L	15-40	33.00 (20.25-41.50)	38.50 (25.50-57.25)	0.164
Total bilirubin concentration, μmol/L	0-23	14.45 (10.45-21.05)	18.05 (11.05-28.35)	0.235
Serum creatinine concentration, μmol/L	57-97	55.00 (48.00-74.00)	67.00 (48.00-111.00)	0.327
CK-MB, ng/mL	0-5	1.29 (1.04-1.73)	2.59 (1.64-4.17)	0.006
Hypersensitive troponin I, ng/mL	0-0.04	0.02 (0.01-0.09)	0.13 (0.02-0.39)	0.005
Prothrombin time, s	9-13	12.70 (11.90-13.95)	13.85 (12.48-15.50)	0.445
Activated partial thromboplastin time, s	25-31.3	28.25 (23.58-30.58)	28.20 (26.68-33.25)	0.103
D-dimer, mg/L	0-0.55	11.76 (2.44-17.59)	20.25 (8.98-61.31)	0.025
FDP, mg/L	0-5	34.14 (10.41-66.67)	79.49 (27.37-116.23)	0.021

Data are presented as median (IQR). COVID-19 = novel coronavirus disease 2019. CK-MB = Creatine kinase-MB. FDP = fibrin degradation products.

oxygen therapy type (oxygen inhalation, high flow nasal cannula, and non-invasive ventilation) between the two groups from the time of onset of symptoms to tracheal intubation.

Clinical outcomes

Among 52 critical COVID-19 patients who received tracheal intubation and IMV, 14

Table 3. Differences in vital signs, blood gas analysis and oxygen therapy before tracheal intubation between successful intubation and extubation failure patients with COVID-19

	All patients (n = 52)	Successful intubation (n = 14)	Extubation failure (n = 38)	*p* Value
Onset of symptom to tracheal intubation, d	18.50 (15.00-23.00)	18.00 (11.5-26.00)	19.00 (15.75-23.00)	0.672
Heart rate, bpm	90.00 (78.25-114.25)	85.50 (75.75-119.25)	92.50 (79.00-112.75)	0.536
MAP, mmHg	93.50 (85.25-103.75)	90.50 (86.75-105.25)	94.00 (80.75-104.25)	0.836
Respiratory rate	32.00 (39.00-42.00)	39.50 (33.50-42.00)	37.50 (31.50-42.25)	0.605
SpO_2, %	80.00 (70.75-85.00)	85.00 (80.00-85.25)	78.50 (67.75-85.00)	0.033
PH	7.45 (7.37-7.49)	7.46 (7.38-7.49)	7.45 (7.36-7.49)	0.397
PaO_2, mmHg	59.50 (51.00-68.00)	65.00 (54.50-70.00)	59.00 (50.00-67.25)	0.901
$PaCO_2$, mmHg	40.00 (35.00-46.75)	41.50 (33.00-46.75)	39.50 (35.75-47.25)	0.278
Ratio of PaO_2 to FiO_2, mmHg	73.00 (59.25-84.75)	84.50 (65.75-95.25)	71.50 (58.50-80.75)	0.040
Lactate, mmol/L	2.10 (1.73-3.08)	2.00 (1.45-3.15)	2.25 (1.80-3.03)	0.219
Oxygen therapy				
Oxygen inhalation	18 (34.62)	5 (35.71)	13 (34.21)	0.919
High flow nasal cannula	40 (76.92)	12 (85.71)	28 (73.68)	0.475
Non-invasive ventilation	27 (51.92)	9 (64.29)	18 (47.37)	0.279

Data are presented as median (IQR) or n (%). COVID-19 = novel coronavirus disease 2019. MAP = mean arterial pressure. SpO_2 = saturation of pulse oxygen. PaO_2 = partial pressure of oxygen. $PaCO_2$ = partial pressure of carbon dioxide. FiO_2 = fraction of inspired oxygen.

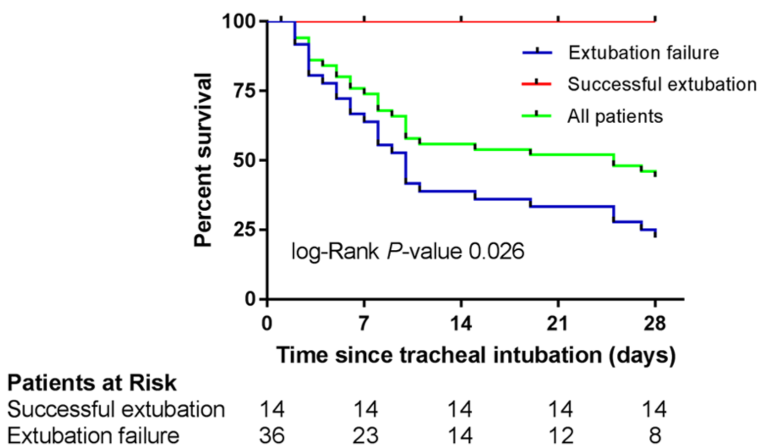

Figure 2. Kaplan-Meier plot of cumulative survival for intubation patients with COVID-19 based on successful extubation compared to extubation failure (Log-Rank *p*-value 0.026). 2 patients died within 24 h after trachea intubation.

(26.9%) patients were successfully extubated within two weeks while 38 (73.1%) patients were not. In the patients who were successfully extubated, the median duration from the time of tracheal intubation to extubation was 11.00 days (IQR, 6.75-13.25). Further, 3 patients were discharged from the hospital, and 11 patients were transferred from the ICU to the common ward and stayed in the hospital for 28 days. Among the 38 patients who were not successfully extubated within two weeks, 5 patients received ECMO and only 1 was successfully withdrawn from the ECMO and still survived till the 28th day. 7 patients out of 10 who underwent a tracheotomy, survived till the 28th day. 23 patients died within 28 days of receiving tracheal intubation, and the median duration from tracheal intubation to death was 5.00 days (IQR, 3.00-9.00). Finally, of the 52 critical COVID-19 patients who received tracheal intubation and IMV, 22 patients (42.3%, 14 patients from successful extubation group and 8 from extubation failure group) survived till the 28th day. The 28-day survival rate was significantly lower in the extubation failure group (21.05%, *P* = 0.026) as compared with that in the successful extubation group (28-day survival rate: 100%) (**Figure 2**).

Discussion

We retrospectively analyzed the data of 52 critical COVID-19 patients administered with tracheal intubation and IMV. Out of the 52 patients, 14 were successfully extubated while 38 failed extubation with a mortality rate of 78.95%. The majority of extubation failure occurred in older patients who were harboring severe hypoxemia coupled with cardiac damage and coagulation dysfunction before being administered tracheal intubation. All the 30 patients who died within 28 days belonged to the extubation failure group while 14 patients in the successful extubation group survived till the 28th day. This confirmed that a better prognosis of patients with trachea intubation depends on the success of extubation. These findings will further enrich the knowledge about the disease and consequently help to improve patients' outcomes and lower the fatality rate.

The high death rate observed in our study was similar to the rate observed in a recent report [3] in which 19 out of the 22 intubated patients in the ICU died. Patients admitted to our center were mostly males (61.54%, 32/52) of median age 63.50 years with fever as the most common symptom (in 92.31% of the patients) and at least one comorbidity (in 65.38% of the patients). The median time from onset to admission to the hospital was 10 days. Median heart rate and median MAP (89 bpm and 99 mmHg respectively) were within the normal range in both successful extubation and extubation failure groups. The patients' baseline characteristics of this study were close to those reported earlier [3, 8, 11]. The respiratory rates were continuously above 30 breaths per minute and SpO_2 was continuously below 93% in both successful extubation and extubation failure groups. These observations demonstrated the occurrence of severe lung injury/ARDS in the patients. Also, our findings indicate that extubation failure occurred to a greater extent in relatively older patients (median age: 67.50 years). In consensus with other reports [8, 15], our observations suggest that older people are at a higher risk of increased mortality.

The pre-tracheal intubation laboratory findings of both the groups showed increased levels of white blood cells and decreased lymphocyte count along with myocardia injury, hepatic injury, kidney injury, and coagulation activation. These abnormalities in laboratory findings were similar to those previously reported in critical COVID-19 patients [1, 3, 8, 11]. Besides these findings, we also observed a more severe level of myocardia injury and coagulation activation in patients of extubation failure group as compared with the patients of successful extubation group. These abnormalities suggest that multiple-organ injuries may be associated with poor outcomes and high mortalities [16, 17].

Tracheal intubation and IMV are the most common treatment options for severe ARDS patients [18-21]. In the present series of cases, the median values of SpO_2 and P/F before tracheal intubation were significantly lower in extubation failure group (SpO_2: 78.50%, P/F: 71.50 mmHg) as compared with those of successful extubation group (SpO_2: 85.00%, P/F: 84.50 mmHg), although the two values in successful extubation group were relatively lower than normal ranges. SpO_2 and P/F were two key markers for evaluating the degree of hypoxemia. A retrospective study showed that the symptoms related to hypoxemia are more common in deceased patients than in recovered patients [15]. This observation may suggest that early intubation in a controlled setting by close monitoring for deterioration of respiratory status is critical for successful weaning in tracheal intubation patients, and the guidelines also suggest the same [18]. According to the frontline physicians taking care of critical COVID-19 patients in Wuhan, tracheal intubation and IMV may have been adversely delayed in some patients, although no conclusive evidence is available to support that observation [22]. Among the involved brain areas, the brainstem was found to be heavily affected [23], a manifestation that might account for the depression of the cardio-respiratory center of the brain. Therefore, we believe that intubation should be timely conducted in patients presenting with the clinical signs of refractory hypoxemia and reduced voluntary breathing [21, 22] to avoid further development of hypoxia.

Besides, our results indicated that extubation success was closely related to saturation of oxygenation before intubation. Therefore, we suggest that other oxygen therapies should be used to improve oxygenation before extubation even though the use of initial oxygen therapy in our patients did not result in the difference in clinical outcomes. Cheung et al. demonstrated that non-invasive ventilation prior to tracheal intubation and IMV is effective in the treatment of severe acute respiratory syndrome (SARS) patients [24]. But patients and clinical physicians have to endure high risks during intubation and ventilation management amid the COVID-19 outbreak [21]. Thus, experts suggested that personal protection and close monitoring of the health status of the involved staff are equally important [25].

However, our study had several limitations. First, a small sample size of 52 patients might not be representative of the total cases diagnosed and treated in Wuhan; therefore, multicenter studies with a large sample size are needed to further validate our results. Second, some of the patients developed consciousness disorders; therefore, medical history could only be acquired from their families, resulting in probable loss of some relevant aspects. Third, some laboratory tests were not carried out in all the patients, and the missed data might lead to bias in clinical characteristics. Finally, except for ventilation support, other medications such as antivirals, corticosteroids, and Chinese traditional medicine also played important roles in the final outcome of the patients. However, these data did not present in our observation. Therefore, more intensive studies are warranted to get a better understanding of the therapeutic effects of these interventions on patients with COVID-19.

In conclusion, we observed high mortality in COVID-19 patients receiving tracheal intubation and IMV; mortality was especially high in elderly patients with non-successful extubation who were suffering from various diseases and multiple organ damage. Successful weaning is used as a predictor for prognosis. These findings have important implications for the timely management of patients infected with SARS-CoV-2. We also found that more severe hypoxemia was associated with extubation failure and poor outcomes. Therefore, we recommend the administration of early tracheal intubation and invasive ventilation to critical COVID-19 patients to normalize oxygenation and avoid secondary multiple organ injuries. The high mortality of this series of intubated cases may be due to delayed intubation, which prolonged the duration of hypoxemia.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhui Yu, Department of Critical Care Medicine, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuchang District, Wuhan 430060, Hubei, P. R. China. Tel: +86-13986095479; Fax: +86-27-88042292; E-mail: yuzhui@whu.edu.cn

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