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Letter to the Editor

Clinical features of critically ill patients with confirmed COVID-19

To the Editor:

We read with great interest the article by Wenjie Yang and colleagues,[1] accepted for publication in the *Journal of Infection*. The authors performed a retrospective multi-center cohort study and presented important data regarding the observation that most patients of 2019 novel coronavirus disease (COVID-19) from Wenzhou city, Zhejiang, exhibited mild infection. However, the information of critically ill patients, especially treated with extracorporeal membrane oxygenation (ECMO), was scare. No study to date has provided evidence that the clinical features of critically ill patients with confirmed COVID-19 from Zhejiang province. We performed a single-centered, retrospective, observational study to investigate the clinical characteristics and ventilation conditions of critically ill patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

From late January to February 23, 2020, 33 critically ill patients in the intensive care unit (ICU) of the First Affiliated Hospital of Zhejiang University who were diagnosed as COVID-19 in accordance with the diagnosis and treatment guidance published by the Chinese government were enrolled in the study.[2] We obtained patients' demographics, epidemiology data, details of laboratory tests, treatments, and ECMO implantation.

The baseline epidemiological characteristics and clinical features of 33 studied patients as classified by with or without ECMO treatment were shown in Table 1. Most of the patients admitted to the ICU were older and had several common comorbid conditions, which demonstrated that age and comorbidities might be the indicators for severely ill one and poor prognosis. Of all patients, the mean age was 65.2±16.6 years, and most of the patients were aged 65 years and older. Of the seven patients who received ECMO, the mean age was 67.0±17.7 years. Twenty-two (66.7%) had underlying comorbidities, involving hypertension (66.7%), diabetes (18.2%), and cardiovascular diseases (18.2%). For the 7 patients who received ECMO, 5 (71.4%) patients had associated comorbidities, including hypertension (4 [57.1%]), cardiovascular diseases (1 [14.3%]), diabetes (1 [14.3%]), chronic obstructive pulmonary disease (1 [14.3%]), malignancy (1 [14.3%]), and liver diseases (1 [14.3%]). In our study, more than half of the critically infected patients were men (22 [66.7%]), especially in ECMO treated patients (6 [85.7%]). Jing Li *et al.*[3] observed men probably had more complicated clinical conditions and worse in-hospital outcomes as compared to women in severe COVID-19 patients. The median time from onset of symptoms to hospital admission was 7 days (IQR 6-10 days) which was longer than Wenjie Yang and colleagues' study.

In terms of baseline laboratory data of severely confirmed COVID-19 patients, three (9.0%) and 22 (66.7%) of 33 patients exhibited leucopenia and lymphopenia, respectively. Platelets levels on admission were lower in patients with ECMO treatment than non-ECMO patients. Also, a recent case report verified the counts of peripheral CD4 and CD8 T cells were both decreased in a 50-year-old man with SARS-CoV-2 infection through the technology of flow cytometric analysis.[4] Specifically, the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) on admission were higher in ECMO treated patients (median AST 38.5U/L [IQR 24.8-75.5]; median ALT 30.5 U/L [IQR 18.8-45.3]) than non-ECMO treated patients (median AST 23.5 U/L [IQR 17.0-36.3], p=0.049; median ALT 17.0 U/L [IQR 14.0-26.3], p=0.034; Table 1). Besides, admission levels of total bilirubin were increased substantially in ECMO treated patients. These abnormalities suggested that SARS-CoV-2 might be related to hepatic injury. However, almost all of the included patients received antivirus treatment, the drug induced liver injury could not be excluded. Huang *et al.* reported that increased level of AST was found in about 62% of the ICU patients in their study.[5] Therefore, damaged liver function is more common in serious COVID-19 patients. Up to now, there has been no sufficient evidence to clarify SARS-CoV-2 as the main reason of damaged liver function. Further studies should concentrate on the reasons of liver function damage in patients with COVID-19. The level of procalcitonin increased in more than 70% of included patients, and most of patients in our study received antibacterial and antifungal agents. One possible explanation for the results may be that many of the critically ill patients were associated with combined infection of bacterial or fungal.

ECMO has been increasingly being used as a rescue treatment for refractory hypoxemia in patients with severe acute respiratory distress syndrome.[6] The initial mode was veno-venous (VV) ECMO in the 7 patients. Initiation of ECMO was accompanied by a significant improvement in PaO_2/fraction of inspired oxygen (FiO_2) ratio, and significant decreases in $PaCO_2$, FiO_2 (Table 2). Research showed too high level of FiO_2 was related to increased production of reactive oxygen-derived free radicals which were noxious to the humans health.[7]

In summary, our data indicated that SARS-CoV-2 infection might cause damage to the immune and liver function of COVID-19 patients. ECMO support was associated with improved ventilation conditions in COVID-19 patients with refractory hypoxemia. The study may be helpful to providing evidence of the appropriate time to initiate ECMO for critically ill patients with COVID-19, and add further evidence for critically ill patients' characteristics.

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Table 1
Demographics and baseline clinical features of 33 COVID-19 patients in the ICU

Parameters	All patients	With ECMO	Without ECMO	*P* value
Number	33	7	26	
Age, y	65.2 ± 16.6	67.0 ± 17.7	64.7 ± 16.6	0.75
Age groups (years)				
≤18	0 (0.0%)	0 (0.0%)	0 (0.0%)	
19-40	4 (12.1%)	1 (14.3%)	3 (11.5%)	
41-65	11 (33.3%)	3 (42.9%)	8 (30.8%)	
≥66	18 (54.5%)	3 (42.9%)	15 (57.7%)	
Sex				0.38
Men	22 (66.7%)	6 (85.7%)	16 (61.5%)	
Women	11 (33.3%)	1 (14.3%)	10 (38.5%)	
Chronic Comorbidities				
Hypertension	22 (66.7%)	4 (57.1%)	18 (69.2%)	0.66
Diabetes	6 (18.2%)	1 (14.3%)	5 (19.2%)	1.00
Cardiovascular diseases	6 (18.2%)	1 (14.3%)	5 (19.2%)	1.00
Chronic obstructive pulmonary disease	1 (3.0%)	1 (14.3%)	0 (0.0%)	0.21
Malignancy	1 (3.0%)	1 (14.3%)	0 (0.0%)	0.21
Renal diseases	2 (6.1%)	0 (0.0%)	2 (7.7%)	1.00
Liver diseases	3 (9.1%)	1 (14.3%)	2 (7.7%)	0.52
Onset of symptoms to hospital admission, median (IQR), d	7 (6-10)	10 (5-13)	7 (6.5-10)	0.53
Blood routine				
Leucocytes, $\times 10^9$/L	10.5 ± 5.8	6.5 ± 4.7	11.6 ± 5.7	0.039*
Increased	15 (45.5%)	1 (14.3%)	14 (53.8%)	
Decreased	3 (9.0%)	1 (14.3%)	2 (7.7%)	
Neutrophils, $\times 10^9$/L	9.1 ± 5.8	5.3 ± 4.2	10.1 ± 5.8	0.050
Increased	19 (57.6%)	1 (14.3%)	18 (69.2%)	
Lymphocytes, $\times 10^9$/L	0.5 (0.45-0.9)	0.4 (0.3-0.7)	0.6 (0.5-1.0)	0.004*
Decreased	22 (66.7%)	6 (85.7%)	16 (61.5%)	
Platelets count, $\times 10^9$/L	180.0(139.0-196.0)	111.0 (99.0-142.0)	189.0 (169.0-201.5)	0.002*
Blood biochemistry				
ALT, U/L	20.0 (14.5-30.0)	30.5 (18.8-45.3)	17.0 (14.0-26.3)	0.034*
Increased	2 (6.0%)	1 (14.3%)	1 (3.8%)	
AST, U/L	25.0 (18.3-40.0)	38.5 (24.8-75.5)	23.5 (17.0-36.3)	0.049*
Increased	8 (24.2%)	3 (42.9%)	5 (19.2%)	
Total bilirubin, μmol/L	11.8 (8.0-18.5)	20.5 (11.8-36.6)	9.6 (7.4-14.7)	0.041*
Increased	4 (12.1%)	1 (14.3%)	3 (11.5%)	
Creatine kinase, U/L	24.0 ± 5.0	26.9 ± 4.9	23.1 ± 4.7	0.079
Increased	9 (30.3%)	4 (57.1%)	5 (19.2%)	
Infection-related biomarkers				
Procalcitonin, ng/mL	0.1 (0.05-0.32)	0.3 (0.1-0.7)	0.1 (0.04-0.2)	0.07
Increased	24 (72.7%)	7 (100.0%)	17 (65.4%)	
Interleukin-6, pg/mL	46.6 (20.5-90.2)	290.6 (96.0-446.5)	38.2 (16.5-74.9)	0.016*
Increased	25 (75.8%)	5 (71.4%)	20 (76.9%)	
hs-CRP, mg/L	45.5 (23.4-86.0)	50.0 (24.2-143.4)	40.0 (22.1-59.0)	0.53
Increased	30 (90.9%)	6 (85.7%)	24 (92.3%)	
Bilateral involvement of chest CT	32 (97.0%)	7 (100.0%)	25 (96.2%)	1.00

Data are presented as mean±SD, median (IQR), or counts (%).
Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; hs-CRP, high-sensitivity C-reactive protein; CT, computed tomograms.
P values denoted the comparison between ECMO treated cases and non-ECMO treated cases. *Significant $p<0.05$.

Table 2
Gas exchange after the commencement of ECMO

Parameters	Pre-ECMO	ECMO day 1	*P* value
FiO_2 (%)	70.0 ± 16.3	37.1 ± 12.9	0.011*
Peak inspiratory pressure, cmH_2O	22.0 ± 4.0	19.3± 6.9	0.299
PEEP, cmH_2O	7.0 ± 0.7	6.7 ± 2.0	0.356
PaO_2/FiO_2 ratio	106.8 ± 48.8	235.7± 120.7	0.042*
SPO_2 (%)	92.9 ± 5.6	94.4 ± 5.0	0.525
PaO_2, mmHg	72.4 ± 33.8	77.5 ± 24.7	0.785
$PaCO_2$, mmHg	46.4 ± 5.9	36.0 ± 1.8	0.005*
Lactate, mmol/L	4.2 ± 4.1	2.3 ± 0.5	0.276

Data are presented as mean±SD.
Abbreviations: ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; PEEP, positive end expiratory pressure.
P values denoted the comparison between pre-ECMO and the first day of ECMO. *Significant $p<0.05$.

Declaration of Competing Interest

The authors of this study declared no conflict of interest.

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