Point-by-Point Response to Reviewers' Comments

Note: our responses are in italic and red.

Reviewer #1:

In case 1: - How would the Authors rule out, if there was no HELLP-syndrome by the pregnant women? Liver enzymes were elevated, Low Platelet number was reported and Disseminant Intravascular Coagulation (DIC) was also present by this case? Covid 19 could be only co-finding, which was then later exacerbated?

Response: Thank you very much for your comments. HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome is a life-threatening condition manifesting in preeclampsia. In our case report, the young pregnant woman developed similar symptoms. However, she did not have a history of hypertensive pregnancy disorders. She took regular antenatal checks, and the results were normal (it has been clarified in the revised manuscript). On the first day she went to the hospital due to fever, her blood pressure was 118/66 mmHg, and her platelet count (160×10^9/L) and hemoglobin concentration (110 g/L) were normal. Her lymphocyte count was 0.884×10^9/L and rapidly reduced to 0.14×10^9/L in the first 24h after admission along with ARDS and low blood pressure, which indicates infection. Although her ALT (142 U/L) and AST (235 U/L) were high on the day of her admission, we think it was due to viral infection rather than HELLP syndrome as up to 58% COVID-19 patients present elevated liver enzymes [1] and she had no history of hypertension during pregnancy. Thus, we speculated that elevated liver enzymes, low platelet number and DIC as well as multiple organ dysfunction during the treatment were complications of COVID-19.

In case 2: What is the Authors opinion, VV-ECMO did have an effect on the right herart failure (RHF)?

Response: We think VV-ECMO contributed to the development of right ventricular failure (RVF). RVF is a common complication which presents in more than half of patients requiring VV-ECMO[2]. The main etiology of it is RV overload [3]. Literature reveals that the non-pulsatile blood flow provided by VV-ECMO can cause sustained

RV overload[4, 5]. Long-term high PEEP ventilation can also result in RV overload. As patients with severe ARDS are advised to maintain a high PEEP (15cm H_2O) after initiating ECMO [6], the risk of RVF in these patients therefore increases. In our case, to improve her oxygenation and alleviate pleural effusion, a relatively high PEEP (16cm H_2O) was applied. After 10 days of ECMO support, the female patient developed RVF. Her RV function gradually improved with decreased PEEP and ECMO flow. Therefore, it is reasonable to suspect that VV-ECMO contributed to the development of RVF.

What were the ECHO parameters of right ventricle? TAPSE? The ventilation pressure (Pinsp) and PEEP were too high during VV-ECMO support. In literature state, that ultra-protective ventilation might have an important role to minimizes the ventilator-induced lung injury. The benefits should be discussed! A structured review of the literature and a table about it would be outstanding and important!

Response: Unfortunately, TAPSE was not recorded in our case report. However, we recorded the right ventricular diameters (RVD) as an ECHO parameter

Hospital Stay	*1*	*2*	*4*	*6*	*9*	*11*	*14*	*17*	*19*	*20*	*23*	*27*	*32*	*37*
Pinsp (cmH_2O)	*32*	*32*	*35*	*35*	*32*	*30*	*28*	*28*	*28*	*28*	*32*	*30*	*23*	*22*
PEEP （cmH_2O）	*16*	*16*	*16*	*16*	*16*	*15*	*12*	*12*	*12*	*12*	*9*	*9*	*9*	*8*
RVD (mm)	*20*	*20*	*22*	*22*	*22*	*20*	*20*	*19*	*22*	*28*	*27*	*25*	*20*	*20*

We applied a relatively high ventilator setting (pinsp, 35 cm H_2O; Vt, 4-6ml/kg; PEEP, 16 cm H_2O) after initiating MV in case one, and we gradually decreased them as the patients' condition improved. The main aim of MV is usually to provide sufficient gas-change while decrease the incidence of ventilator-induced lung injury (VILI). Protective lung ventilation, which targets a static inspiratory pressures (plateau pressure) of less than 30 cm H_2O and a Vt of 4-8 ml/kg, is the current

standard strategy for mechanical ventilation [7]. However, in case one, fibreoptic bronchoscopy found massive frothy sputum in case one, and she developed respiratory acidosis, indicating severe pleural effusion and insufficient oxygenation. To improve oxygenation and pulmonary diffusion, a relatively high pinsp was necessary, and we gradually decreased pinsp as VV-ECMO was applied and the oxygenation was improved to target the protective lung ventilation. For PEEP, currently there is not an optimal level established. A meta-analysis showed that there is no significant survival difference between higher PEEP and lower PEEP in the first 72h of MV among patients with ARDS. However, in patients with a PaO_2/FiO_2 ratio lower than 200 mmHg, higher PEEP was associated with reduction in mortality, while higher PEEP was associated with increased mortality in patients with a PaO_2/FiO_2 higher thant 200 mmHg [7]. It indicates that patients with severe ARDS can benefit from a higher PEEP. Recently, a newly emerged concept called ultra-protective ventilation strategy attracts much interest. It introduces a lower Vt(<4ml/kg) with a plateau pressure of ≤25 cmH_2O to minimize the risk of VILI. However, as it may not provide sufficient gas-change, the risk of hypoxia may increase. Recently, a retrospective study with 62 ARDS patients requiring VV-ECMO found that the ultra-protective ventilation was feasible, but no survival benefit was observed [8]. Here we summarized the possible pros and cons of lung-protective ventilation and ultra-protective ventilation.

	Lung protective ventilation	*Ultra-protective ventilation*
VT	*4-8 ml/kg [9]*	*<4 ml/kg [8]*
PEEP	*Based on $PEEP/FiO_2$ [10]*	*a high PEEP level*
Plateapressure	*< 30cmH_2O*	*≤25 cmH_2O*
Advantages	*It can decrease the risk of VILI while provide sufficient gas-change*	*It can minimize the risk of VILI.*
Disadvantages	*It cannot completely avoid VILI.*	*It can increase atelectasis and may result in severe*

ventilation/perfusion mismatch; it needs a higher ECMO flow to maintain oxygenation

In general, there are too many typos throughout the text.

Response: We have checked and corrected the typos throughout the text.

Reviewer #2:

Major revision: The case report does not simply list the treatment history of the case, but through the diagnosis and treatment analysis of the case, certain conclusions (or experience and lessons) can be drawn from it for clinical reference and even guide clinical practice. There is currently some encouraging evidence that the use of ECMO in COVID-19 is clinically beneficial. Both patients were treated with ECMO, but the results were different. Why did this result occur? The author lacks an analysis of the reasons and draws appropriate conclusions from it.

Response: Thank you very much for your instructive comments. Both patients were treated with VV-ECMO and weaned off VV ECMO successfully. However, the results were different. One has been discharged from the hospital with normal vital signs and laboratory tests, while the other is still on ventilation support and may require a lung transplantation due to pulmonary fibrosis. Several factors may lead to the outcome difference between these two patients. One of the factors is age. It was shown that older people had an increased risk of developing pulmonary fibrosis following SARS or MARS-induced ARDS [11, 12]. Similarly, a multi-center retrospective study recently revealed that older patients with COVID-19 (45.4±16.9 vs 33.8±10.2 years) were more prone to develop pulmonary fibrosis[13]. This should be taken into consideration since that ECMO is such a resource-intensive and expensive equipment. Another possible reason is the timing of MV. Case 1 was mechanically ventilated immediately after oxygen therapy failure, while Case 2 underwent high-concentration oxygen therapy for 10 days and experienced shortness of breath for about a day before MV support. Although oxygen therapy is a lifesaving technique for

patients with hypoxia, it has been demonstrated that continuous high-concentration oxygen therapy can cause lung injury[14]. There is probably a survival benefit to apply MV earlier when oxygen therapy cannot provide satisfying oxygenation, and this needs to be investigated in the future. Besides, studies have shown that the high transpulmonary pressure caused by shortness of breath can also damage his lungs[15]. In addition, hospital-acquired infection (HAI) may contribute to their opposite outcomes as well. In case 1, no bacteria were detected in blood culture, while in case 2, streptomonas maltophilia was detected in blood culture after removing ECMO. This pathogen may further aggravate inflammation in his lungs and damage his pulmonary function.

Minor revision: The running title has a too broad meaning and it is recommended to modify it.

Response: We have changed our running title to "Two cases of COVID-19-related ARDS treated with ECMO".

It is suggested to supplement the final COVID-19 virus nucleic acid reexamination results of these two patients. If so, it is recommended to provide the results of the lungs' CT images of the patients before discharge.

Response: Thank you very much for your advice. We have provided the COVID-19 virus nucleic acid results and the lungs' CT images of the patients in the revised manuscript. However, the CT images before weaning off ECMO in case one are unfortunately missing and we therefore made a comparison of the chest images between day 30 and day 40.

It is recommended to add references to line 99.

Response: The sentence has been rephrased and a proper reference has been placed.

Line 118-122, the Chief complaints should be concise, and part of the content can be transferred to the History of present illness.

Response: We have moved some part of the content to the History of present illness.

Line 125, When did she get back from Wuhan?

Response: She went to Wuhan, Hubei province on 17th, January 2020 and returned to Zhongshan city, Guangdong province on 25th, January 2020. We have clarified this in

the revised manuscript.

Line 144-150, it is suggested to improve the important contents of physical examination, especially the auscultation of both lungs.

Response: More details have been added to Physical examination in the revised manuscript.

Line 261-264, because the patient has a history of hypertension and coronary heart disease, it is recommended to supplement the patient's blood pressure and.

Response: The blood pressure at admission was 129/71mmHg. There was no pathologic sound detected from cardiac auscultation. We have added this in the revised manuscript.

Line 412-415, it is recommended to add references.

Response: A proper reference has been placed.

Line 420-423, it is recommended to add references. It is recommended that the references list all the authors.

Response: Line 420-423 is a conclusion of our data. All authors have been listed in the References.

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