EXTRACORPOREAL MEMBRANE OXYGENATION FOR COVID-19 ASSOCIATED SEVERE ACUTE RESPIRATORY DISTRESS SYNDROME

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COVID-19 caused significant mortality worldwide, including in Vietnam. This study aimed to evaluate the effectiveness of Extracorporeal membrane oxygenation (ECMO) in the treatment of COVID-19 patients with acute respiratory distress syndrome (ARDS). From January 1, 2022 to March 31, 2022, the COVID-19 hospital admitted 395 critical patients, including 10 patients required veno-venous Extracorporeal membrane oxygenation (VV-ECMO). This descriptive study revealed relatively high survival rate of 60% (6/10 patients) with the median duration of ECMO was 11.5 days. The study group's SOFA and RESP scores were 6 and 4, respectively. Time from symptom onset to mechanical ventilation, duration of NIV and/or HFNC before mechanical ventilation, time from symptom onset to ECMO of the study patients were 9.5, 0 and 11.5 days, respectively. The most common complication in ECMO patients was nosocomial infection (70%), in addition to bleeding, embolism, or both at the same time. This preliminary research showed that ECMO was effective in the management of acute respiratory distress syndrome in patients with COVID-19.

Keywords: COVID-19, ECMO, ARDS, Vietnam.

I. INTRODUCTION

The COVID-19 pandemic has been spreading rapidly across the globe with the mortality rate in severe and critical cases up to 54.65%.[1] The SARS-COV-2 virus leads to complicated lung injury from mild to critical, progress to ARDS in some cases. Severe and critical patients have a high mortality rate, especially in ARDS patients due to prolonged hypoxemia, even with timely invasive ventilation. ECMO is considered the last resort for respiratory support, with the maintenance of extracorporeal membrane oxygen and the implementation of a pulmonary protective ventilation strategy.

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Studies of ECMO on COVID-19 patients from 2019 to date have shown mixed results. From the center of Wuhan, the first reports on the clinical characteristics and treatment of Covid patients in 2020 show a high mortality rate in ECMO cases (from 83.33% to 100%).[2,3] The study by Dognon, N., et al. in the second epidemic wave also showed that the mortality rate of COVID-19 patients who received ECMO intervention in the second epidemic wave was higher than in the first wave (69% vs 58%).[4] However, these studies were aggregated on a small number of patients on small scale. In addition, COVID-19 patients are often given non-invasive ventilation or prolonged HFNC ventilation before intubation, ECMO indication is only suggested when others fail.

Until 2021, there are specific guidelines on indications for ECMO intervention in COVID-19

patients, the trend of early ECMO intervention when meeting the criteria helps to improve mortality.[5,6] Recent studies have shown ECMO reduces mortality in critically ill COVID-19 patients.[7,8]

COVID-19 causes a systemic manifestation due to endothelial damage, which leads to COVID-19-associated coagulopathy (CAC): hypercoagulability associated microthrombosis was similar to disseminated intravascular coagulation (DIC), thromboembolism on the one hand, but could cause bleeding due to intravascular leakage on the other.[9] This makes the clinical presents and coagulation complications of ECMO patients more diverse. According to the studies of Durak, K. et al., and Ripoll, B., et al. on patients with COVID-19 undergoing ECMO intervention, coagulation events encountered both bleeding and embolism, or both at the same time.[10,11]

In Vietnam, the VV-ECMO intervention for critically ill COVID-19 patients has been conducted since the first epidemic wave, but there are no specific research reports on the effectiveness of this method. Therefore, we conducted this study to evaluate the results of using extracorporeal membrane oxygenation (ECMO) in the treatment of acute respiratory distress syndrome (ARDS) in patients with COVID-19.

II. SUBJECT AND METHODS

This study recruited patient, who were confirmed COVID-19 by reverse transcription – polymerase chain reaction (RT-PCR) technique and received VV-ECMO in intensive care units from January 2022 to March 2022 at the COVID-19 Hospital. Patients were selected based on updated 2021 guidelines from the Extracorporeal Life Support Organization:[5]

Indication for VV-ECMO: when having 1 of the following criteria: 1) P/F ratio < 50 for > 3 hours; 2) P/F ratio < 80 for > 6 hours; 3) pH < 7.25 with $PaCO_2$ ≥ 60 mmHg for > 6 hours to achieve the goal of setting Pplat ≤ 32 cmH_2O, despite increasing respiratory rate to 35 breaths/min.

- Contraindications for VV-ECMO:

+ Time of mechanical ventilation > 10 days;

+ Age ≥ 71 years old;

+ Severe co-morbidities: Chronic kidney disease stage ≥ 3, cirrhosis, dementia, previous neurological disease with irreversible function, advanced cancer, irreversible progressive lung disease, diabetes uncontrolled diabetes with multiple organ complications, severe exhaustion, severe peripheral vascular disease, inability to do normal activities;

+ Severe multi-organ failure;

+ Severe acute brain injury

+ Severe immunosuppression.

+ Contraindicated with systemic anticoagulants.

+ When VV-ECMO was initiated, cannulation was performed at the bedside, using Seldinger technique or open cut-down technique.

The detailed information of each patient before and after was collected by physicians using standard form: demographic data, medical history, underlying medical condition, symptoms, laboratory… The technical procedures and treatment protocols comply with the guidelines of the Ministry of Health.

Data collection was carried out after treatment for the patient, without interfering with the treatment process to affect the benefits for the patient. All information collected will be kept confidential and used for research purposes only.

+ Data processing: The data were processed using SPSS statistical software, mainly describe percentages and compare medians.

- Main research criteria:

Primary endpoints: outcome of patients with ECMO intervention and clinical characteristics of the study group.

Secondary endpoints: Events in ECMO patients.

- Definition of event:

Nosocomial infections: infections acquired after admission, manifesting 48 hours after admission
Thrombosis events: thrombosis at any site in the body, thrombosis event was diagnosed on CT scan or vascular ultrasound
Bleeding events: Bleeding from any site of the body.
Thrombosis with bleeding events: both thrombosis and bleeding occur simultaneously.

III. RESULTS

1. Outcomes and clinical characteristics of the study patients

10 critically ill COVID-19 patients who were eligible to conduct VV-ECMO were included. A half of the patients were male (50%). The median age was 32, with the oldest was 52 years old and the youngest was 18 years old.

The median duration of ECMO was 11.5 days. The number of survival cases with ECMO intervention was 6 (60%).

Table 1. Clinical and laboratory characteristics of patients before ECMO intervention.

	Total (n=10)	Survival (n=6)	Death (n=4)
Characteristics of respiratory support before ECMO intervention			
Symptom onset to mechanical ventilation (days)	9.5	5.5	12
Duration of NIV and/or HFNC before mechanical ventilation (days)	0	0	3.5
Duration of mechanical ventilation before ECMO (days)	1	1	3
Symptom onset to ECMO (days)	11.5	8	17.5
Arterial blood gas			
pH	7.32	7.26	7.36
pCO_2	53.3	59.4	40.7
pO_2	65.5	75.1	51.5
P/F ratio (mmHg)	70	78.5	62.5
Scale for severity			
SOFA	6	6	5
APACHE II	14	14	16.5
RESP	4	6	0.5

SOFA and APACHE II scores were 6 and 14, respectively.

The RESP scores to assess the survival of patients with VV-ECMO intervention in the study group (total), survival group, and death group were 4, 6, and 0.5, respectively.

Table 2. Characteristics of risk factors for severe progression of the study group

		Total (n=10)	Survival (n = 6)	Death (n = 4)
Vaccination of COVID-19	Administer 2 or more doses of vaccine	5	3	2
	No vaccination	5	3	2
Risk factors for severe progression	Obesity	2	1	1
	Diabetes	2	1	1
	Hypertension	3	2	1
	Pregnancy	3	2	1
	Long-term corticosteroid use	1	0	1
	Hepatitis B	1	0	1

5/10 patients in the study group have not been vaccinated against COVID-19.

All 10/10 study patients had risk factors for severe progression, including obesity, pregnancy, diabetes, hypertension, long-term corticosteroid use, and hepatitis B.

2. Complications in patients with ECMO

Table 3. Complications in patients with ECMO

Events	Total (n=10)	Survival (n = 6)	Death (n = 4)
Nosocomial infections	7	5	2
Thrombosis events	2	0	2
Bleeding events	3	1	2
Thrombosis with bleeding events	1	1	1

The most common event in the patients undergoing ECMO was nosocomial infection, 70% (7/10 patients).

Thrombosis events occurred in 2 patients: one patient had pulmonary embolism and one patient had lower extremity deep vein thrombosis.

Bleeding events were encountered in 3 patients: the bleeding sites encountered were pulmonary (one patient), oropharyngeal (one patient), and ECMO cannula (2 patients).

Thrombosis with bleeding events in 1 patient: lower extremities deep vein thrombosis of and pulmonary bleeding, oropharyngeal bleeding.

IV. DISCUSSION

The epidemic period from January 2022 to March 2022 is the time when the epidemic took

place the most in Hanoi, our study collected 10 patients, and the obtained results have helped strengthen the evidence on the effectiveness of ECMO treatment for critically ill COVID-19 patients.

Hall, C.A., et al. conducted a multi-institutional analysis with a large sample of 505 COVID-19 patients who received ECMO interventions in 45 different centers, showing a survival rate of 39.5%, the mean age in the survival group was 44 years old, lower than the death group (51 years old). The mean duration of ECMO intervention in the study was 18 days.[8]

Ramanathan, K. et al. conducted data analysis on all studies of COVID-19 patients who suffered from ECMO with a minimum sample size of 10 (22 studies). The total number of cases included in the data was 1986 with the majority being VV – ECMO (98.6%) between December 2019 and January 2021, mean ECMO duration was 15.81 days; the survival rate was 62.6%. The study also confirmed that the survival group had a lower age than the death group.[7]

Our study showed the survival rate was 60% (6/10 patients), higher than Hall, C.A. et al., and is equivalent to the analytical data of Ramanathan, K. et al. The duration of ECMO intervention was shorter (11.5 days). However, with a small sample size (10 cases) conducted in a short period of 3 months, the difference between the two groups of survival and death could not be assessed. Patients undergoing ECMO were indicated early as soon as the criteria were met, so the survival rate was high.

The study of Li, X. et al. on 31 patients, comparing early ECMO intervention at the time of meeting the criteria with the intervention group after meeting the criteria 24 hours, showed an improvement in the 60-day mortality after ECMO was early intervention within 24 hours when meeting ECMO intervention criteria.[6] Our study group all received early ECMO intervention within 24 hours when eligible.

Also, the study by Li, X. et al., showed time from symptom onset to mechanical ventilation, NIV and/or HFNC duration before intubation, time from symptom onset to ECMO of the study group was 19 days, 3 days, 22 days, respectively. There was no difference either in the early or late intervention group. In our study, the results were lower.

The study of Hermann, M. et al., when assessing the risks related to the outcome of patients receiving ECMO intervention, showed SOFA and RESP scores were 5.9 and 4, respectively. The survival rate of the study group was 59%; there was no difference on these two scales between the survival group and the deceased group. The duration of invasive mechanical ventilation before ECMO did not differ between the 2 groups.[12] Our study showed similar results with SOFA and RESP scores of the study group were 6 and 4, respectively.

When analyzing the risk factors for severe progression in ECMO patients, we found that all patients had the risk of severe progression: obesity, pregnancy, diabetes, hypertension, long-term corticosteroid use, hepatitis B.[13] Especially, all 3 pregnancies case were in the last 3 months of pregnancy, elective cesarean section, endotracheal intubation , and ECMO intervention. There are also cases of multiple comorbidities, the obese patient was recorded with a BMI of 40, concurrently with type I diabetes mellitus.

The most common event in the study group was nosocomial infection (7/10), accounting for 70% of patients. The nosocomial infection rate in our study was higher than research by Marcus, J.E., V.G. Sams, and A.E. Barsoumian

(37.3%) and research by Diaz, R.A. et al. (51.4%). However, the sample sizes of these two studies were larger and conducted over a longer period.[14,15]

Research by Durak, K., et al. analyzed 17 COVID-19 patients who received VV - ECMO intervention, and found that coagulation events were seen in 12 patients, in which thrombosis events were seen in 7 patients, bleeding events occurred in 10 patients. The bleeding group had a longer PT index and lower platelet count than the non-bleeding group.[10] Ripoll, B., et al observed 30 patients with VV - ECMO intervention, there were 13 patients with thrombosis, of which 5 patients progressed to serious bleeding (cerebral hemorrhage, pulmonary hemorrhage), the group without embolism had 01 case of severe oropharyngeal bleeding.[11]

In our study, all three complications of thrombosis, bleeding, and thrombosis with bleeding were noted. 3/4 patients died due to coagulopathy, of those 1 case of VV-ECMO developed acute pulmonary embolism 1 day after the end of ECMO intervention with hemodynamic disturbances and severe hypoxemia; subsequently, patient was treated by intravenous fibrinolysis and received ECMO intervention again, but did not survive. The remaining two cases had serious bleeding in the lung, oropharyngeal, and lower extremities, and deceased in the context of hemorrhagic shock caused by severe coagulopathy and one patient had lower extremity deep vein thrombosis and pulmonary bleeding at the same time.

V. CONCLUSION

The surviving rate was 60% with median duration of ECMO was 11.5 days. The most common event in the study group was nosocomial infection, all three complications of thrombosis, bleeding, and thrombosis with bleeding were noted.

The use of ECMO had initially shown good results in the treatment of acute respiratory distress syndrome in COVID-19 patients. Further studies on this issue are needed.

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