The Pattern and Distribution of Ventilatory Defects after Extracorporeal Membrane Oxygenation in Survivors of Leptospirosis with Acute Respiratory Distress Syndrome: A Single-center Cross-sectional Study

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ABSTRACT

Background and Objective. Pulmonary hemorrhage and acute respiratory distress syndrome (ARDS) are complications of severe leptospirosis with higher mortality rates. These are indications for initiating extracorporeal membrane oxygenation (ECMO). Given the improved survival of leptospirosis patients undergoing ECMO, little is known about the expected pulmonary function, including the presence and severity of possible ventilatory defects following these complications and intervention. This study aimed to determine the pattern and distribution of ventilatory defects in patients who underwent ECMO for severe leptospirosis with ARDS and survived.

Methods. This is a cross-sectional study that reviewed all patients who underwent ECMO for severe leptospirosis and ARDS at the National Kidney and Transplant Institute from its initiation in 2018 up to December 2021. The primary outcomes measured were the presence and severity of ventilatory defects by spirometry. Secondary outcomes included the clinical profile, laboratory findings, radiologic features, duration on mechanical ventilation, and duration on ECMO. Stata17 was used for data analysis.

Results. Among 14 patients meeting the inclusion criteria, 11 were male with a mean age of 30 years (SD, 6.2). Using spirometry, 13 had a restrictive ventilatory defect, while only 1 had a normal result. Of the 13 patients, 9 had mild disease, 2 each had moderate, and moderately severe disease. A lower platelet count, lower PaO_2/FiO_2 ratio (PFR), higher SOFA score, and longer duration of days on ECMO were noted in the group with ventilatory defect. Meanwhile, longer duration of days on mechanical ventilation (MV) and ECMO, higher procalcitonin, and higher APACHE-II scores were noted in patients with moderately severe restrictive ventilatory defect.

Conclusions. This study suggests that restrictive ventilatory defect may be seen among patients who survived severe leptospirosis and ARDS after undergoing ECMO.

Keywords: ventilatory defect, extracorporeal membrane oxygenation, severe leptospirosis, acute respiratory distress syndrome

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INTRODUCTION

Leptospirosis is one of the most common zoonotic human infections caused by the *Leptospira* species, which occurs after exposure to a contaminated environment with animal fluids such as flood waters. This disease remains a public health concern in tropical and temperate regions, with an estimated 1.03 million cases annually worldwide, leading to 58,900 cases of mortality.[1] It is endemic in the Philippines and was reported to have 1,598 cases in 2021, with 169 (10.5%) fatal cases.[2] Severe leptospirosis can involve multiple organ system failure, especially the kidneys, lungs, and central nervous system, with the latter two being significant predictors of mortality.[3]

The incubation period of leptospirosis may range from 2 to 28 days. After incubation, patients present with fever, conjunctival suffusion, myalgia, calf tenderness, jaundice, renal failure, pulmonary hemorrhage, and respiratory failure.[4] The incidence of pulmonary complications among leptospirosis cases ranges from 20% to 70%. Its main pulmonary complication is alveolar hemorrhage, which manifests as dyspnea and hemoptysis. Severe pulmonary hemorrhage leading to ARDS in leptospirosis has been associated with excessive mortality rates as high as 55%.[5]

Given these fatal consequences, novel therapies such as ECMO are gaining more evidence in the management of pulmonary hemorrhage and ARDS in leptospirosis. In a study by Delmas et al. on patients with leptospirosis who were admitted to the intensive care unit (ICU), 41 patients required mechanical ventilation (MV), 5 of whom underwent ECMO, and 4 (80%) survived after the said therapy.[6] Improved outcomes were also seen in a local study conducted by Barrameda et al. that showed the use of ECMO and Hemoperfusion (HP) in patients with severe leptospirosis with pulmonary hemorrhage and multiple organ failure to have a significantly lower 28-day mortality rate, with the probability of dying reduced to as low as 6 times lower compared to those who did not undergo ECMO and HP.[7]

With increased survival among this specific population, little is known about the outcomes of the impairment of their pulmonary function. A study by Oh et al. showed that 11.3% of ECMO survivors were newly diagnosed with chronic respiratory diseases (CRD) after 12 months of ECMO therapy. However, the study was mostly based on chart reviews with ICD codes and did not seek information regarding the diagnostic tool used, such as chest CT scan or pulmonary function testing.[8] In another study by Ego et al. on patients who underwent ECMO for ARDS due to COVID-19 infection, long-term diffusion disorders persisted without other remarkable pulmonary function test abnormalities after 6 months of survival. However, the population included in this study is limited to those afflicted with COVID-19, a disease known to cause long-term pulmonary problems on its own, despite the severity.[9]

There is limited published local data describing pulmonary function outcomes in patients recovering from ARDS and severe leptospirosis. This study aims to characterize the pattern and distribution of ventilatory defects among survivors of severe leptospirosis with ARDS who received ECMO support at the National Kidney and Transplant Institute (NKTI), the country's leading referral center for leptospirosis and the institution with the largest ECMO patient registry.

METHODS

A cross-sectional study was done, which included patients aged 19 years and older with severe leptospirosis and ARDS (as defined by the Berlin Criteria), who were admitted to the ICU and placed on MV and ECMO from January 2018 to December 2021. Only patients with spirometry data before discharge or <6 months after discharge were included. We excluded those who had significant comorbid illness, such as heart failure New York Heart Association NYHA class IV, chronic obstructive pulmonary disease (COPD) requiring oxygen therapy, liver cirrhosis, peripheral vascular disease with at least below-the-knee amputation, and those who died from the disease.

Ethics and protocol approval were obtained from the NKTI Institutional Review Board and Research Ethics Committee (NKTI-IRB-2022-050). All patients with severe leptospirosis who underwent ECMO from its introduction in the institution's introduction of ECMO in 2018 until December 2021 were considered for enrolment. The charts of 31 patients were reviewed from the Medical Records Section. Seven were excluded for having died of the disease, while 8 were unable to do spirometry. Of the remaining 16 eligible patients, 2 had their spirometry done >6 months after their discharge and were also excluded from the study. The remaining 14 patients met the inclusion criteria and were subsequently enrolled.

Data were collected from the charts and medical record reviews using a data abstraction form. The following information were extracted: age, sex, comorbidities, history of smoking in pack years, vital signs, initial laboratory results (complete blood count, arterial blood gas, hsCRP, procalcitonin, BUN, creatinine, total bilirubin, sodium, potassium), Radiographic features (number of quadrants affected), total duration of MV, total duration of ECMO, and spirometry results were collected. Spirometry testing was done at the institution according to the ATS/ERS/ACCP Guidelines, and the results were interpreted following local guidelines in reporting spirometry tests and lung volume studies.[10] Data collected were then encoded in a Microsoft Excel file.

The primary outcome of the study is to identify the presence and distribution of ventilatory defects. Secondary outcomes include the identification of clinical profile, laboratory, radiologic features, duration on MV, and duration

on ECMO, along with the possible association of these with the presence and severity of ventilatory defects.

Continuous variables, including age, smoking history, initial laboratory parameters, duration of MV, duration of ECMO, APACHE-II score, SOFA score, and Murray score, FEV1, FVC, FEV1/FVC, and DLCO, were summarized as means with their corresponding standard deviation. Categorical data, such as pattern and severity of ventilatory defect from spirometry, were presented as frequency and percentage. STATA MP 17 was used for data analysis. We assessed the possible correlation between several continuous independent variables and the severity of ventilatory defect, using multiple ordinal logistic regression analyses. Subgroup analyses based on the severity of ventilatory defect and clinical characteristics of patients were done using the Kruskal-Wallis test.

RESULTS

Out of 31 patients with severe leptospirosis and ARDS who underwent ECMO, 14 fulfilled the inclusion criteria. Only 1 patient had a normal pulmonary function test result, while the rest were noted to have ventilatory defects (93%).

As reported in Table 1, the mean age of patients was 30 years (SD,6.2), and the majority were male (11). Sex and presence of a ventilatory defect were not found to be significantly associated (p = 0.786). Patients did not have comorbidities such as hypertension, diabetes, previous COPD, or asthma. The median number of pack-years of smoking history was 4.75 years (IQR 7.38).

At baseline laboratory findings highlighted in Table 2, all patients presented with leukocytosis and elevated BUN, creatinine, and hsCRP levels. Meanwhile, thrombocytopenia, lower initial PFR, and elevated procalcitonin were noted in patients with ventilatory defect; however, significance could not be determined due to the lack of variability. The majority (10 of 14) presented with infiltrates on all four quadrants on admission. The lung quadrants affected and the presence of a ventilatory defect were not significantly associated (p = 0.714). On presentation, both groups had a similar mean APACHE-II and Murray scores, while the SOFA score was lower in the normal group.

As shown in Table 3, the pulmonary function test showed that the mean value of FEV1 among patients was 2.49 L/s (0.54), while the mean FVC was 2.75 L (0.58). Among all patients, the mean FEV1/FVC was 90.64 (4.8), with the mean DLCO of 13.53 ml/min/mmHg (2.1).

Table 1. Demographic and Clinical Characteristics by the Presence of Ventilatory Defect

Characteristics	All, N = 14	Normal, n = 1	With ventilatory defect, n = 13	*p*-value
	Frequency; Mean (SD)			
Age (years)	30 (6.2)	30.0	30 (6.47)	
Sex				
Male	11 (79%)	1 (100%)	10 (77%)	0.786
Female	3 (21%)	0	3 (23%)	
Smoking history (pack-years) (Median and IQR)	4.75 (IQR 7.38)	5.0	4.5 (IQR 8.5)	

Table 2. Baseline Laboratory Findings, Clinical Profile, and Radiologic Features by the Presence of Ventilatory Defect

Characteristics	All, N = 14	Normal, n = 1	With ventilatory defect, n = 13	*p*-value
	Frequency; Mean ± SD			
WBC (10^9/L)	14.1 (8.0)	14.6	14.0 (8.3)	
Platelet (10^9/L)	74.4 (64.7)	205.0	64.4 (54.8)	
Creatinine (mg/dl)	7.3 (3.1)	8.3	7.2 (3.2)	
BUN (mg/dl)	76.0 (37.0)	89.0	75.0 (8.3)	
hsCRP (mg/L)	212.8 (96.6)	208.8	213.1 (100.5)	
Procalcitonin (ng/ml)	269.9 (820.8)	2.83	290.5 (850.6)	
Pa-O_2/Fi-O_2	85.1 (46.4)	127.1	81.9 (46.7)	
SOFA score	15.3 (2.6)	12.0	15.5 (2.5)	
APACHE-II score	17.4 (2.8)	17.0	17.5 (2.9)	
Murray score	3.2 (0.2)	3.0	3.2 (0.2)	
Chest X-ray				
3 quadrants	4 (29%)	0.0	4 (30%)	0.714
4 quadrants	10 (71%)	1 (100%)	9 (70%)	
Use of Inotropes	13/14 (93%)	1 (100%)	12/13 (92%)	

Table 3. Spirometry Results

Characteristics	All, n = 14 [Mean (SD)]
FEV1 (L/s)	2.49 (0.54)
FVC (L)	2.75 (0.58)
FEV1/FVC (%)	90.64 (4.8)
TLC (L)	3.7 (0.71)
DLCO (ml/min/mmHg)	13.53 (2.1)

Table 4. Distribution of Ventilatory Defects among Patients (N = 14)

Pattern	All, n = 14 Frequency (%)
Normal	1 (7%)
Obstructive	0
Restrictive	13 (93%)
Mild	9 (64%)
Moderate	2 (14%)
Moderately Severe	2 (14%)
Severe	0
Very Severe	0
Mixed	0

Interpretation of the pulmonary function tests summarized in Table 4 shows that most (13 of 14) had a restrictive ventilatory defect pattern, and only 1 showed normal results. None presented with an obstructive or mixed ventilatory defect. The majority of those with restrictive ventilatory patterns were mild (9), while 2 each were moderate and moderately severe.

Our data showed that patients with a ventilatory defect had a longer duration of ECMO, almost twice that of the normal group. They had a lower initial PFR and a higher SOFA score (Table 5).

As emphasized in Table 6, patients with moderately severe defects had a longer duration on MV and on ECMO, more than twice compared to those in the mild and moderate group. The initial PFR was also inversely proportional to the severity of the restrictive ventilatory defect, with the lowest mean value (55.0, SD18.4) seen in the moderately severe group. Only the APACHE-II score among the severity-of-illness scores showed a proportional increase as the severity of the defect increased. However, there was no significant difference across the three groups (p-values >0.05). Other Illness severity scores, i.e., the SOFA and Murray scores, were comparable across varying degrees of ventilatory defect.

Table 5. Duration on MV and ECMO, Severity of Illness Scores by the Presence of Ventilatory Defect

Characteristics	All, N = 14	Normal, n = 1	With ventilatory defect, n = 13
	Mean ± SD		
Duration on MV (days)	11.6 (8.6)	10.0	11.7 (8.9)
Duration on ECMO (days)	9.1 (8.3)	5.0	9.4 (8.6)
Initial PaO_2/FiO_2	85.1 (46.4)	127.1	81.9 (46.7)
Murray Score	3.2 (0.2)	3.0	3.2 (0.2)
SOFA Score	15.3 (2.6)	12.0	15.5 (2.5)
APACHE-II Score	17.4 (2.8)	17.0	17.5 (2.9)

Table 6. Clinical and Laboratory Characteristics by Severity of Restrictive Ventilatory Defect

Characteristics	Mild, n = 9	Moderate, n = 2	Moderately severe, n = 2	*p*-value*
	Mean ± SD			
Duration on MV (days)	9.1 (2.9)	9.0 (1.4)	26.0 (19.8)	0.200
Duration on ECMO (days)	7.0 (2.2)	5.5 (0.7)	24.0 (18.4)	0.071
Initial PaO_2/FiO_2	89.6 (54.0)	74.0 (18.4)	55.0 (18.4)	0.604
Murray Score	3.2 (0.2)	3.3 (0.4)	3.3 (0.4)	0.986
SOFA Score	15.3 (2.7)	16.5 (0.7)	15.5 (3.5)	0.942
APACHE-II Score	16.7 (3.0)	18.0 (0.0)	20.5 (2.1)	0.156
WBC (in 10^9/L)	14.3 (10.0)	11.6 (4.4)	15.5 (1.2)	0.600
Platelets (in 10^9/L)	64 (61.4)	72.5 (70.0)	58 (28.3)	0.834
Crea (in mg/dl)	7.3 (3.6)	7.6 (0.2)	6.5 (3.8)	0.971
BUN (in mg/dl)	85.1 (38.6)	55.5 (13.4)	49.0 (49.5)	0.452
hsCRP	211.9 (98.4)	286.8 (150.5)	144.7 (30.4)	0.418
Procalcitonin	55.2 (95.8)	44.6 (23.3)	1595.0 (2141.4)	0.212
Smoking (pack-years)	7.3 (6.7)	2.0 (2.8)	4.5 (6.4)	0.405

**Comparisons were performed using the Kruskal-Wallis test*

The anticipated direct correlation between illness severity and the extent of ventilatory impairment was not demonstrated using these scoring systems. However, further studies with larger sample sizes are warranted to confirm these findings.

DISCUSSION

The Institute started performing veno-venous ECMO in 2018 as a life-saving intervention among patients with severe leptospirosis complicated by pulmonary hemorrhage and ARDS. ECMO is indicated since these complications bring about hypoxemic respiratory failure with a high mortality rate of at least 55% despite optimal therapy with antibiotics, corticosteroids, and renal replacement therapy.[11] Since then, 34 patients underwent the procedure, and 26 (76%) were able to survive. Among survivors, much is still unknown about their outcomes, especially about their resulting pulmonary function following the complications of the disease and this extracorporeal intervention.

Chronic respiratory diseases (CRD) are noted to develop among survivors of ECMO therapy. In a cohort study by Oh et al., CRD were diagnosed in 11.3% of ECMO survivors after 12 months post- intervention. The prevalent post-ECMO CRD among adult survivors was asthma (6.1%) and COPD (3.0%), which are primarily obstructive lung diseases.[8] In contrast, our study showed that the predominant ventilatory pattern among survivors is a restrictive ventilatory defect (13/14). This may be because they included patients with various underlying diseases as the indication for ECMO therapy, including those with cardiovascular diagnoses such as cardiac arrest or cardiogenic shock. It is more plausible that the underlying disease has more effect on the development and type of ventilatory defect present, rather than the intervention itself. As for our patients, the restrictive pattern noted may be explained by the specific pulmonary pathology in severe leptospirosis. Non-inflammatory vasculopathy was noted on autopsy findings, with immunohistochemical detection showing endothelial cell junction disruption and opening of intercellular gaps, thereby presenting with edema and bleeding affecting the alveolar lining.[11] Because this pathology, specific to leptospirosis, affects the distal lung parenchyma involved in gas exchange, a restrictive ventilatory pattern can be seen in this set of post-ECMO patients. The results demonstrate a difference in the major ventilatory pattern noted in this study compared to previous literature. This highlights the importance of including the underlying disease prompting ECMO initiation in the analysis of the development and type of ventilatory defect in post-ECMO patients.

The severity of a restrictive ventilatory defect can be related to the underlying etiology and its subsequent damage to the lung parenchyma. In a retrospective cohort study on post-ECMO patients by von Bahr et al., the total duration on MV ($p < 0.001$) and ECMO ($p < 0.001$) correlated with the degree of parenchymal damage.[12] In a retrospective cohort study including a total of 6536 patients, it was shown that longer duration of MV and ECMO therapy failed early weaning of these interventions and are at higher risk for mortality and complete recovery.[13]

Limitations of the Study

There is limited data on the pulmonary sequelae after survival from severe leptospirosis with ARDS who underwent ECMO. This study is limited by its cross-sectional study design and limited number of participants; no conclusion can be directly made, and a larger cohort study is needed to address these gaps. However, the researchers believe that the results are still important in identifying risk factors that affect the prognosis and quality of life among this subset of patients.

CONCLUSION

This study suggests that restrictive ventilatory defect may be seen among patients who survived severe leptospirosis and ARDS after undergoing ECMO. Further data could be obtained by comparing baseline spirometry results with follow-up pulmonary function tests conducted after six months to one year to evaluate the persistence of ventilatory defects.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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