

Electrocardiographic Findings and Incidence of New-onset Atrial Arrhythmia among Patients with Severe Leptospirosis who Underwent Veno-venous Extracorporeal Membrane Oxygenation: A Single Center Cross-sectional Study

Bryan Leonard M. Quizon, MD,¹ Areefah A. Adiong, MD,² Manuel John A. Dayao, MD³ and Emil Mari C. Follosa, MD⁴

¹Division of Pulmonary Medicine, Department of Medicine, Philippine General Hospital, University of the Philippines Manila, Manila, Philippines

²Division of Internal Medicine, National Kidney and Transplant Institute, Quezon City, Philippines

³Division of Cardiovascular Medicine, Department of Medicine, Philippine General Hospital, University of the Philippines Manila, Manila, Philippines

⁴Department of Adult Cardiology, Philippine Heart Center, Quezon City, Philippines

ABSTRACT

Background. Leptospirosis is a zoonotic disease caused by *Leptospira* species that remains endemic in the Philippines. In severe cases, patients present with multiple organ system failure such as acute renal failure and acute respiratory distress syndrome (ARDS) requiring renal replacement therapy, mechanical ventilation, and novel treatment modalities such as extracorporeal membrane oxygenation (ECMO). Cardiac complications such as atrial arrhythmia also occur in cases of severe leptospirosis leading to worse outcomes. There is limited data on the electrocardiographic findings in patients with severe leptospirosis undergoing ECMO along with the incidence of new-onset atrial arrhythmia while managed on this intervention with unique hemodynamic system.

Objective. This study aims to determine the baseline electrocardiographic (ECG) findings and incidence of new-onset atrial arrhythmia among patients with severe leptospirosis during veno-venous (V-V) ECMO.

Methods. A cross-sectional study among patients with severe leptospirosis and ARDS who underwent V-V ECMO was conducted at the National Kidney and Transplant Institute. Primary outcome was defined as the presence of new-onset atrial arrhythmia during ECMO. Secondary outcomes included in-hospital mortality, length of hospital stay, duration of mechanical ventilation, duration of ECMO, and development of thrombotic events.

Results. Among 31 patients included, 90.3% (n = 28) were male and median age was 33.48 ± 10.0 years. The most common ECG finding was atrial fibrillation with an incidence of 32.3% (n = 10), half of which occurred before ECMO, while the other half were noted after cannulation. During ECMO, the incidence of new-onset atrial arrhythmia was found to be at 19.4% (n = 6). Patients with new-onset atrial arrhythmia had higher white blood cell, total bilirubin, BUN, creatinine, APACHE-II scores, use of dopamine, lower platelet count and lower PaO₂/FiO₂ ratio. Two patients (33.33%) died



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Corresponding author: Bryan Leonard M. Quizon, MD
Division of Pulmonary Medicine
Department of Medicine
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: bmquizon@gmail.com
ORCID: <https://orcid.org/0009-0009-8212-0543>

among those with new-onset atrial arrhythmia, while five patients (20%) died in the other group. There was no noted thrombotic events such as stroke among the groups and no difference on the duration on mechanical ventilator, ECMO and hospital stay.

Conclusion. New-onset atrial arrhythmias are the most common ECG findings during V-V ECMO among patients with severe leptospirosis with an earlier occurrence in this population post-cannulation. Atrial fibrillation is noted as the most common electrocardiographic finding in this population. This study demonstrated a higher mortality among patients with new-onset atrial arrhythmia during ECMO for severe leptospirosis, with no statistical difference.

Keywords: atrial arrhythmia, severe leptospirosis, extra-corporeal membrane oxygenation

INTRODUCTION

Leptospirosis is a zoonotic disease caused by *Leptospira* species after exposure to a contaminated environment.¹ In the Philippines, a total of 1,598 cases in the year 2021 were reported with 10.5% leading to mortality.² In severe cases, patients present with multiple organ system failure, more commonly in the kidneys and the lungs that would require renal replacement therapy and mechanical ventilatory support respectively. In most severe complications such as pulmonary hemorrhage and acute respiratory distress syndrome (ARDS), novel treatment modalities such as extra-corporeal membrane oxygenation (ECMO) are gaining evidence in their management. In a study in France by Delmas et al., 4 out of 5 (80%) of their patients with severe leptospirosis who required ECMO survived after the therapy.³ This result was also supported by a local study by Barrameda et al. which showed that patients who underwent ECMO and hemoperfusion (HP) had significantly lower mortality reduced to 6 times less compared to those who did not undergo these treatment modalities.⁴

Severe leptospirosis may manifest with cardiovascular involvement such as hypotension, atrial arrhythmia, conduction blocks, and nonspecific ventricular repolarization abnormalities. These complications are under-reported and poorly understood. Multiple factors are postulated to contribute to cardiac involvement in this disease. Direct cardiac involvement such as myocarditis and myocardial failure were reported in autopsies, however indirect factors such as electrolyte abnormalities, sepsis, and severe acidosis are heavily implicated as well. Despite the lack of clear pathophysiologic mechanism, electrocardiographic (ECG) abnormalities and hemodynamic instability undoubtedly remain prominent in severe cases.⁵

Few studies report the electrocardiographic alterations in patients with leptospirosis. In a cross-sectional study by

Sacramento et al. in Brazil, 68.2% of leptospirosis patients had abnormal ECG findings noted on the 1st 24 hours of their admission. Based on their results, atrial fibrillation (AF) was noted as the most frequent finding which was present in 10.8% of their patients.⁶ However in another study by Skerk et al., the most common finding among their cohort was non-specific ventricular repolarization disturbances (13.4%). Among their patients, AF was only regarded as the 4th most frequent electrocardiographic finding with an estimated incidence of 6.18%.⁷ Generally, detection of new-onset AF is associated with increased morbidity, such as risk for ischemic stroke and in-hospital mortality, especially among the critically ill patients at the Intensive Care Unit (ICU).⁸

There is limited data concerning the development of new-onset atrial arrhythmias in the background of both severe leptospirosis with ARDS and use of V-V ECMO. This study aims to determine the baseline ECG findings and incidence of new-onset atrial arrhythmia among patients with severe leptospirosis and ARDS during V-V ECMO.

METHODS

Study Design

A descriptive cross-sectional study was done 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.

Study Participants

This study included patients aged 19 years and above admitted from January 2018 to December 2021 for severe leptospirosis with ARDS at the ICU and treated with MV and ECMO. Severe leptospirosis was defined according to the latest local clinical practice guidelines and ARDS was classified using the Berlin Criteria.¹ Those with significant comorbidities such as heart failure NYHA class IV, COPD requiring oxygen therapy, peripheral vascular disease with at least below-the-knee amputation, and decompensated liver cirrhosis were excluded. As a pilot study, no sample size was set, and instead, all patients admitted from the initiation of V-V ECMO in the institution up to December 2021 were reviewed for inclusion.

Ethical Considerations

Ethics and protocol approval was obtained from the NKTi Institutional Review Board and Research Ethics Committee (NKTi-IRB-2022-075). A total of 31 patients were included from the list reviewed from the Medical Records Section. All of them met the criteria for inclusion and were included in the analysis.

Data Collection

Data were collected using a data abstraction form. Demographic information included were age, sex, occupation, place of residence, body mass index, smoking history,

alcohol use, comorbidities such as hypertension, diabetes, hyperthyroidism, stroke, chronic kidney disease (CKD), myocardial infarction or coronary artery disease. Clinical and laboratory data were acquired through review of medical records and these included: complete blood count, creatinine, blood urea nitrogen (BUN), total bilirubin, sodium, potassium, magnesium, calcium, HSCRP, procalcitonin, arterial blood gas, 2D-echocardiography, electrocardiography, APACHE-II scores, use of vasopressors, duration on MV and ECMO, and length of hospital stay.

Primary outcome was defined as the presence of new-onset atrial arrhythmia during ECMO. Secondary outcomes included in-hospital mortality, length of hospital stay, use and type of vasopressor, days on mechanical ventilation, days on ECMO, and presence of complications of atrial arrhythmia such as ischemic stroke.

Data Analysis

Demographic information were summarized using descriptive statistics. Categorical data were reported as

frequency and percentage, while continuous variables were presented as mean with standard deviation. The incidence of new-onset atrial arrhythmia was reported as frequency and proportion. Mann-Whitney U-test was used to compare numerical variables of between patients with and without new-onset atrial arrhythmia. Fisher-exact test was used to test the association of categorical characteristics and outcomes with the presence of new-onset atrial arrhythmia. SPSS version 25 was used for data analysis at 5% level of significance.

RESULTS

Among 31 patients with severe leptospirosis and ARDS who underwent ECMO, majority were male (90.3%) and the mean age of all patients is 33.48 ± 10.0 years. (Table 1) Most patients lived in urban areas (96.8%) and majority were employed (58.1%) with possible occupational exposure to the pathogen (wet market, construction site, flooded streets). Only two patients had comorbid conditions, with one having

Table 1. Baseline Demographics and Characteristics of Patients by Presence of New-onset Atrial Arrhythmia

Characteristics	All (n=31)	With New-onset Atrial Arrhythmia (n=6)	Without Atrial Arrhythmia (n=25)	P-value
Age (in years)	33.48 $\pm$ 10.0	35.3 $\pm$ 13.6	33.0 $\pm$ 9.4	0.802 [#]
Sex				
Male	28 (90.3%)	6 (100%)	22 (88.0%)	0.372 [§]
Female	3 (9.7%)	0 (0.0%)	3 (12.0%)	
Occupation				
None	13 (41.9%)	2 (33.3%)	11 (44.0%)	0.634 [§]
Employed	18 (58.1%)	4 (67.7%)	14 (56.0%)	
Construction	12 (38.7%)	4 (66.7%)	8 (32.0%)	
Market Vendor	3 (9.7%)	0 (0.0%)	3 (12.0%)	
Driver/Delivery	3 (9.7%)	0 (0.0%)	3 (12.0%)	
Place of residence				
Urban	30 (96.8%)	6 (100%)	24 (96.0%)	0.618 [§]
Rural	1 (3.2%)	0 (0.0%)	1 (4.0%)	
BMI (Asia Pacific)	22.2 $\pm$ 2.9	21.8 $\pm$ 3.2	22.3 $\pm$ 3.0	0.841 [#]
Underweight	4 (12.9%)	2 (8.0%)	2 (33.3%)	0.118 [§]
Normal	13 (41.9%)	12 (48.0%)	1 (16.7%)	
Overweight	9 (29.0%)	6 (24.0%)	3 (50.0%)	
Obese	5 (16.1%)	5 (20.0%)	0 (0.0%)	
Smoking history				
No	16 (51.6%)	15 (60.0%)	1 (16.7%)	0.056 [§]
Yes	15 (48.4%)	10 (40.0%)	5 (83.3%)	
Packyears	3.1 $\pm$ 2.7	3.8 $\pm$ 3.0	1.5 $\pm$ 0.7	0.136 [#]
Alcohol use				
No	16 (51.6%)	3 (50.0%)	13 (52.0%)	0.930 [§]
Yes	15 (48.4%)	3 (50.0%)	12 (48.0%)	
Comorbidities				
Without	29 (93.5%)	6 (100%)	23 (92.0%)	0.645 [§]
With	2 (6.5%)	0 (0.0%)	2 (8.0%)	
Hypertension	1 (3.2%)	0 (0.0%)	1 (4.0%)	
Hyperthyroidism	1 (3.2%)	0 (0.0%)	1 (4.0%)	

[#] Mann-Whitney U-test, [§] Fisher-exact test

Table 2. Baseline Laboratory Values and Clinical Features of Patients by Presence of New-onset Atrial Arrhythmia

Characteristics	All (n=31)	With New-onset Atrial Arrhythmia (n=6)	Without Atrial Arrhythmia (n=25)	P-value
Blood Chemistry				
WBC (in 10 ⁹ /L)	15.6 ± 7.3	19.9 ± 6.3	14.6 ± 7.2	0.064 [#]
Platelet (in 10 ⁹ /L)	88.2 ± 82.9	68.2 ± 38.7	93.0 ± 90.3	0.783 [#]
Creatinine (in mg/dL)	7.8 ± 2.7	9.1 ± 1.7	7.5 ± 2.8	0.260 [#]
BUN (in mg/dL)	89.6 ± 33.0	118.0 ± 25.6	82.9 ± 31.2	0.009 [#]
TB (mg/dL)	9.1 ± 5.7	12.1 ± 4.9	8.4 ± 5.7	0.080 [#]
Na (mEq/L)	133.5 ± 8.6	132.3 ± 10.5	133.7 ± 8.3	0.599 [#]
K (mEq/L)	3.9 ± 0.8	4.3 ± 0.8	3.8 ± 0.8	0.161 [#]
Mg (mmol/L)	2.3 ± 0.6	2.4 ± 0.2	2.2 ± 0.7	0.553 [#]
Ca (mmol/L)	7.4 ± 1.3	7.1 ± 1.8	7.5 ± 1.2	0.653 [#]
HSCRP (mg/L)	199.6 ± 95.9	192.0 ± 106.7	201.5 ± 95.5	0.841 [#]
Procalcitonin(ng/ml)	67.0 ± 76.5	41.6 ± 35.2	73.1 ± 82.8	0.484 [#]
PaO ₂ /FiO ₂	96.1 ± 53.9	60.8 ± 18.1	104.6 ± 56.3	0.028 [#]
2D echo				
EF (%)	53.5 ± 15.7	63.1 ± 13.1	51.1 ± 15.6	0.078 [#]
LA enlargement				
Yes	2 (6.4%)	0 (0.0%)	2 (8%)	0.671 [§]
No	28 (90.4%)	6 (100%)	22 (88%)	
LV enlargement				
Yes	11 (35.5%)	2 (33.3%)	9 (36%)	0.867 [§]
No	19 (61.3%)	4 (66.7%)	15 (60%)	
Severity Score				
APACHE-II score	21.8 ± 4.5	24.8 ± 4.5	21.0 ± 4.3	0.087 [#]
Use of vasopressor				
0	2 (6.4%)	1 (16.7%)	1 (4%)	0.416 [§]
1	15 (48.5%)	1 (16.7%)	14 (56%)	
2	8 (25.8%)	3 (50%)	5 (2%)	
3	4 (12.9%)	1 (16.7%)	3 (12%)	
4	1 (3.2%)	0 (0.0%)	1 (4%)	
5	1 (3.2%)	0 (0.0%)	1 (4%)	
Type of vasopressor				
Norepinephrine	29 (93.5%)	5 (83.3%)	24 (96%)	
Dopamine	13 (41.9%)	4 (66.7%)	9 (36%)	
Dobutamine	7 (22.6%)	1 (16.7%)	6 (24%)	
Epinephrine	2 (6.4%)	0 (0.0%)	2 (8%)	
Vasopressin	1 (3.2%)	0 (0.0%)	1 (4%)	

[#] Mann-Whitney U-test, [§] Fisher-exact test

a history of hypertension and the other being diagnosed with hyperthyroidism on admission. None of those included had diabetes, myocardial infarction or coronary artery disease, stroke, or CKD. Table 1 presents the demographic profile of patients showing no significant difference among the two groups.

Baseline laboratory exam findings are presented in Table 2. Mean white blood cell count, total bilirubin, creatinine, BUN, and APACHE-II scores were higher among patients with new-onset atrial arrhythmia. There was also a higher use of dopamine (66.7%) in patients with new-onset atrial arrhythmia as compared to the those who did not present

with it (36%). Baseline platelet count and PaO₂/FiO₂ ratio was also lower in patients presenting with atrial arrhythmia. There was no difference with the measured electrolyte levels between the two groups. Among these data, there was a significant difference when it came to the higher BUN ($p = 0.009$) and lower PaO₂/FiO₂ ratio ($p = 0.28$) that was noted in patients with new-onset atrial arrhythmia during ECMO. There was no difference in the baseline 2D echo findings among the two groups.

The baseline electrocardiographic findings and their distribution are shown in Table 3. Across all patients, atrial arrhythmia was most common (38.7%) with AF having the

Table 3. Baseline Electrocardiographic Findings of Patients

	Frequency (%)
ECG Findings	
Normal Sinus Rhythm	9 (29.0%)
Sinus Tachycardia	9 (29.0%)
Non-specific ST-T Wave Changes	7 (22.6%)
ST-T Wave Changes Suggestive of Ischemia	6 (19.4%)
Incomplete Right Bundle Branch Block	1 (3.2%)
Non-specific Intraventricular Conduction Defect	1 (3.2%)
1 st Degree AV Block	5 (16.1%)
Left Atrial Abnormality	1 (3.2%)
Left Ventricular Hypertrophy by Voltage	1 (3.2%)
Atrial Arrhythmia	12 (38.7%)
Supraventricular Tachycardia	2 (6.5%)
Before Cannulation	1
After Cannulation (New-onset)	1
Atrial Fibrillation	10 (32.3%)
Before Cannulation	5
AF in Rapid Ventricular Response	4
AF in Controlled Ventricular Response	1
After Cannulation (New-onset)	5
AF in Rapid Ventricular Response	4
AF in Controlled Ventricular Response	1

highest incidence among its types (32.3%). This is followed by sinus tachycardia (29%) and a normal sinus rhythm (29%). Among those presenting with atrial arrhythmia, half ($n = 6$) of which were considered new-onset, with a mean time of occurrence at 9.6 hours from ECMO cannulation, while the other half were noted at baseline on admission.

The comparison of in-hospital outcomes among the two groups are presented in Table 4. There was a higher incidence of in-hospital mortality in those with new-onset atrial arrhythmia (33.3%) compared to those without atrial arrhythmia (20%). However, analysis using Fisher-exact test showed no significant difference between the reported in-hospital mortality with the current sample size. There was also no significant difference in the length of hospital stay, duration on mechanical ventilation, and duration on ECMO among the two groups. There were no noted complications such as ischemic stroke even on patients presenting with new-onset atrial arrhythmia.

DISCUSSION

This study showed that atrial arrhythmia (38.7%) was the most common ECG finding among patients with severe leptospirosis who underwent V-V ECMO in this institution. Half of these were new-onset with an incidence of 19.6%. Our results were consistent with the findings of Li et al. in their retrospective cohort study which showed that as high as 30.5% may experience significant atrial arrhythmias post-ECMO cannulation that would warrant pharmacologic or electrical intervention.⁸ Interestingly, there was an earlier occurrence of atrial arrhythmia after ECMO initiation in this population with a mean hours of onset at 9.6 hours which occurred sooner compared to the median time of 1.7 days compared to their study.⁸ They also reported that advanced age, male sex, and use of norepinephrine were independent risk factors for the development of new-onset atrial arrhythmia.^{8,9} However their cohort included patients placed on V-V ECMO for various causes, most of which were due to primary pulmonary infections.

In a review by Millar et al., a systemic inflammatory response (SIRS) documented by elevated cytokines was noted on patients undergoing V-V ECMO as the patient's blood is exposed to the non-epithelialized surface of the circuit leading to widespread activation of the innate immune system.¹⁰ In this milieu of cytokine response, elevated IL-6 level was specifically postulated as a potential inciting factor for atrial arrhythmias in this hemodynamic setting. Chweich et al. suggested the contribution of augmented cytokine response for atrial arrhythmia based on the findings that elevated IL-6 in AF was also associated with other cohorts such as patients with coronary artery disease.¹¹ However, this earlier occurrence in our study may be unique to this subset of patients as severe leptospirosis is also independently associated with an elevated cytokine reaction. In a systematic review by Senavirathna et al., they reported that cytokines such as IL-5, IL-6, IL-8, and IL-10 were elevated among severe leptospirosis patients with severe pulmonary hemorrhage, and IL-6 was associated with more fatal outcomes.¹² It might be worthwhile to look at if this double augmentation of inflammatory response is mainly responsible for driving the high incidence of atrial arrhythmia in this subset of patients. In our institution, patients with severe leptospirosis are given antibiotics along with immunosuppression with steroids and cyclophosphamide. Documentation of IL-6 levels may be

Table 4. Association of New-onset Atrial Arrhythmia and In-hospital Outcomes

Characteristics	All (n=31)	With New-onset Atrial Arrhythmia (n=6)	Without Atrial Arrhythmia (n=25)	P-value
Days on MV	13.6 ± 8.3	12.8 ± 6.5	13.7 ± 8.8	0.980 [#]
Days on ECMO	10.0 ± 6.8	10.3 ± 4.9	9.9 ± 7.2	0.650 [#]
Length of hospital stay, days	26.6 ± 16.3	22.5 ± 11.1	27.6 ± 17.4	0.900 [#]
In-hospital mortality	7 (22.6%)	2 (33.3%)	5 (20.0%)	0.483 [§]

[#] Mann-Whitney U-test, [§] Fisher-exact test

useful in prognostication of outcomes such as arrhythmia and mortality, and use of other immunosuppression specifically targeting IL-6 may be considered for further study among this population.

Our study also reported a higher frequency of dopamine use as an additional vasopressor in the group with new-onset atrial arrhythmia (66.7% vs 36%), with the limitation that we were unable to document the dose given before its onset. Dopamine use in patients with septic shock has a known association with increased risk of arrhythmia.¹³ Our study supports these previous findings hence the use of dopamine should be reconsidered in this subset of patients. The recommendation of the surviving sepsis guidelines on the use of a non-catecholamine, vasopressin, in reducing the requirements of norepinephrine may be more logical and safer to reduce the risk of atrial arrhythmias among patients with severe leptospirosis undergoing V-V ECMO.¹³

Among patients with new-onset atrial arrhythmia, a significantly higher BUN ($p = 0.009$) and lower $\text{PaO}_2/\text{FiO}_2$ ratio ($p = 0.28$) was reported in our study. These may be attributed to a more severe degree of renal failure and lung injury, reflecting the consequence of SIRS leading to multi-organ system failure among these patients. In-hospital mortality was also higher among patients with new-onset atrial arrhythmia (33.3% vs 20%), however statistical analysis showed no significant difference among the two groups likely due to the small sample size of our study. This is in contrast with the reports of Li et al. where in-hospital mortality was significantly higher in V-V ECMO patients with new-onset atrial arrhythmia and showed, through multivariate logistic regression, that these atrial arrhythmias independently increase the odds of in-hospital death (OR 2.21).⁸ Among the secondary outcomes, there were no reported events of ischemic stroke and there was no difference in the length of hospital stay, days on MV, and days on ECMO between those with and without new-onset atrial arrhythmia. These findings should be revisited in a larger study since the lack of significant difference in our results may be due to the limited number of patients who underwent ECMO in the institution. Furthermore, the study findings apply only to patients with severe leptospirosis and should not be generalized.

CONCLUSION

New-onset atrial arrhythmias are the most common electrocardiographic findings during V-V ECMO among patients with severe leptospirosis with an earlier occurrence in this population post-cannulation. Atrial fibrillation is noted as the most common electrocardiographic finding in this population.

Patients with new-onset atrial arrhythmia have higher BUN, use of dopamine, and lower $\text{PaO}_2/\text{FiO}_2$ ratio. This study demonstrated a higher mortality among patients with new-onset atrial arrhythmia during ECMO for severe leptospirosis, with no statistical difference.

Given the limited sample size and the highly specific patient cohort, the findings should not be generalizable to broader patient populations. A larger cohort is recommended to address the limitation of this study. However, due to the few data concerning the development of new-onset atrial arrhythmias in the background of both severe leptospirosis with ARDS and treatment with V-V ECMO, the researchers believe that our findings are important in identifying factors which can prevent this cardiac complication and limit the mortality in this specific population.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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