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Case Report

Therapeutic Plasma Exchange (TPE) in Severe Leptospirosis- Application, Factors Affecting Its Life-Saving Benefits and Outcome: A Case Series from Sri Lanka

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Abstract

Background: Leptospirosis is a globally prevalent zoonosis with significant morbidity and mortality, especially in tropical regions like South Asia. In its severe form, the disease often leads to multiorgan dysfunction, with pulmonary haemorrhage being a major cause of death. Evidence supporting specific treatments for severe leptospirosis with pulmonary involvement remains limited. Recent studies suggest that immunomodulatory therapies, such as therapeutic plasma exchange (TPE), may offer survival benefits. This case series explores the application and outcomes of TPE in patients with severe leptospirosis at a tertiary care hospital in Sri Lanka. **Methods:** We studied a case series involving 10 patients with confirmed severe leptospirosis and multiorgan involvement, from September 2021 to October 2022. All patients received standard care, including intravenous antibiotics and methylprednisolone. TPE was initiated in nine patients based on clinical severity, particularly in the presence of pulmonary haemorrhage. Clinical, laboratory, and radiological data were collected from patient records and follow-up. Leptospirosis diagnosis was confirmed by ELISA IgM testing. TPE decisions were made by a multidisciplinary team. **Results:** Of the nine patients who received TPE, seven survived (77.8%). Pulmonary haemorrhage was the primary indication for TPE in all the cases. All patients had multiorgan involvement: renal failure (90%), hepatic dysfunction (60%), and myocarditis (70%). Mortality was associated with inotropic-dependent myocarditis and mechanical ventilation at TPE initiation. Patients requiring intubation had a 50% mortality rate, compared to 14.3% in those who were not intubated. Non-survivors also had significantly elevated lactate levels (>4 mmol/L) and worsening acid-base status. Four patients required dialysis: three survived. Clinical severity scores increased from admission (mean 3.78) to TPE initiation (mean 4.44), and no patient showed improvement prior to TPE. **Conclusion:** Early initiation of TPE may be lifesaving in severe leptospirosis, particularly when performed before irreversible cardiopulmonary failure. The combined use of TPE and corticosteroids may provide additional benefit by mitigating immune-mediated tissue injury. These findings support further investigation into the timing and patient selection criteria for TPE in severe leptospirosis, particularly in resource-limited settings.

Keywords: leptospirosis; pulmonary haemorrhages; myocarditis; therapeutic plasma exchange

1. Introduction

Leptospirosis has been recognised as the most widespread zoonotic disease globally [1]. It infects 1 million patients, causes 58,000 fatalities, and 2.9 million disability adjusted life years annually worldwide [2]. The disease is particularly prevalent in South Asia, the Asia Pacific, and Latin America [3].

Sri Lanka experienced many significant outbreaks over the past few decades, with a notable outbreak occurring in 2008, during which 7,421 cases were reported to the Epidemiology Unit of Sri Lanka [4]. The case fatality rate during that outbreak was 3%.

The pathogenic genus *Leptospira interrogans* has around 250 serovars categorized into 23 serogroups [5]. Transmission to humans occurs through direct contact with infected animal tissue or bodily fluids, or indirectly from environmental contamination with the pathogen, entering through breaches in the skin or mucosal surfaces.

The clinical manifestations of leptospirosis in humans can vary from a mild, self-limiting acute febrile disease to a severe, life-threatening disorder that involves multiple organ dysfunction [6]. Acute kidney failure, pulmonary haemorrhages, myocarditis, pancreatitis, and multiorgan dysfunction syndrome are among the severe, life-threatening systemic manifestations [4]. A proportion of infected individuals will develop severe illness with multi-organ failure for reasons that remain inadequately explained. Current understanding proposes that both pathogen-related factors (infecting serovar/species, inoculum size) and host-related factors (immunological response) contribute to this variation [7].

Pulmonary involvement from Leptospirosis has a high case fatality rate and is the predominant cause of mortality associated with the disease. Immune pathways are pivotal in the pathophysiology of leptospiral pulmonary haemorrhage [8]. Evidence for effective treatment methods for severe leptospirosis with pulmonary haemorrhages is limited [8]. Immunomodulation with plasma exchange, intravenous immunoglobulin, or glucocorticosteroids may be beneficial in the management of severe leptospirosis [9]. There are reports that indicate the effective application of plasma exchange in leptospirosis [5]. Additionally, Herath N. et al. conducted observational research indicating that patients who received TPE alongside standard therapy exhibited a "possible" higher survival rate [10].

Our report describes a series of patients with severe leptospirosis who were admitted to the Teaching Hospital in Peradeniya (THP), Sri Lanka, over one year and treated with therapeutic plasma exchange (TPE), resulting in a promising outcome in the majority of patients.

2. Methodology

2.1. Patients, Diagnoses and Basic Treatments

The study comprises 10 patients with life-threatening severe leptospirosis and multi-organ involvement who were treated according to the guidelines for severe leptospirosis based on a clinical severity score. All 10 patients received methyl prednisolone, and nine patients received plasma exchange as a therapeutic modality. The data were collected over a period of one year, from September 2021 to October 2022.

Information regarding social and demographic factors, clinical manifestations, examination results, investigations, and treatment was obtained through direct interviews with patients and their relatives during hospital stays, follow-up clinic visits, and from hospital records. The ELISA IgM test for Leptospirosis was used to confirm the diagnosis in all 10 patients.

Sociodemographics included age, gender, and area of residence, and clinical data included exposure history, premorbid health conditions, duration of fever, and additional systemic complaints such as dyspnoea, headache, vomiting, abdominal pain, bleeding, urine output, and examination findings such as pulse rate, blood pressure, and crepitations in the lung bases. The laboratory investigation includes a complete blood count, liver and kidney biochemical profiles, serum electrolytes, troponin levels, venous blood gas analysis, chest radiography, and 2D echocardiography as warranted by the clinical presentation. These investigations were reviewed just before the TPE decision.

All patients were treated with intravenous antibiotics effective for leptospirosis, including ceftriaxone, doxycycline, and benzyl penicillin. All patients received IV methylprednisolone upon achieving a clinical severity score of 2, as described in the previous publication [11]. The treating

physicians determined the choice to provide these therapies based on the clinical severity of the condition, including pulmonary haemorrhages and involvement of other systems. We included all patients with leptospirosis who underwent TPE during the study period.

2.2. Identification of Multiple System Involvement

The identification of pulmonary haemorrhages was based on respiratory distress with blood-gas-based type I respiratory failure, or CXR findings, which didn't provide any other explanation except for pulmonary haemorrhages along with other supportive investigation findings, such as falling haemoglobin level and platelet count. Involvement of other systems was based on appropriate investigations such as ECG, cardiac enzymes, etc. Some of the patients received blood and platelet transfusions, and the management decision was made on a case-by-case basis by a multidisciplinary team in the Intensive Care Unit (ICU).

2.3. Therapeutic Plasma Exchange (TPE)

Ownership and expertise of TPE, also known as plasmapheresis, fall under the purview of transfusion physicians in Sri Lanka. The procedure is performed only in an ICU bed, according to the guidelines of the American Society of Apheresis (ASFA). The TPE machines utilize continuous flow, which follows automated centrifuge-based technology, and each procedure typically lasts approximately 3 hours. The procedure of TPE is used to treat diseases caused by pathogenic antibodies, immune complexes or other macromolecules found in the plasma. Notably, the ideal characteristics of a substance to be removed by TPE should be a large molecular weight, distribution in the intravascular space, and a prolonged half-life. The patient's plasma is separated using an automated platform and replaced with 5% Albumin, Saline, or fresh-frozen plasma. The principal adverse effect is hypocalcaemia. However, transient hypotension, allergies, and even life-threatening anaphylaxis are common adverse reactions related to the replacement fluid used in the procedure. In Sri Lanka, TPE procedures were initiated by the pioneers of the National Blood Transfusion Service (NBTS) in the early 1990s and were done manually. Generally, for leptospirosis, 2 or 3 sessions of TPE are adequate.

Consent: Written informed consent for publication of anonymized clinical details was obtained from the patients or their legal guardians.

3. Results

The number of males was nine, and only one patient was female (Table 1). The youngest patient was 25 years old, while the eldest patient was 65 years. All the patients were from the Kandy District of the hilly Central Province. Nine patients had a significant exposure history to the environment of leptospirosis.

Table 1. Demographic Characteristics of 10 patients.

Data	Distribution	Number, and %
Age	0-25yrs	1 (10%)
	26-50yrs	6 (60%)
	51-75yrs	3 (30%)
Gender	Male	9 (90%)
	Female	1
Significant Exposure history	Yes	9 (90%)
	No	1

Patients are labelled chronologically for identification (Table 2). Four patients had no comorbidities, while 2 had diabetes (Patients No. 3 and 10), and 1 of the diabetes patients had chronic

kidney disease and ischemic heart disease (Patient No. 3). Only one patient had a history of alcohol consumption (Patient No. 6). Patient number 9 had Bronchial asthma.

Table 2. General condition, multiple system involvement, clinical severity score at admission and day of application of TPE with clinical severity score and outcome.

Patient No, Age, Gender	Day of illness on admission	Day of Illness at TPE	Poor general condition	Hematology	Pulmonary	Cardiac	Renal	Hepatic	Clinical Score on Admission	Clinical Score at TPE	Outcome
1-53M	4	6	+	+	-	+	+	-	4	5	
2-49F	3	4	+	-	-	+	-	+	3	4	
3-57M	5	6	-	+	+	-	+	+	4	4	
4-37M	3	4	-	+	-	-	+	+	3	4	
5-40M	10	11	-	+	-	-	+	+	3	4	
6-44M	3	4	+	+	+	+	+	-	5	5	
7-43M	4	8	-	+	-	+	+	-	3	4	
8-45M	4	Not done	+	+	-	+	+	+	5	-	
9-25M	2	3	-	+	+	+	+	-	4	4	Died
10-65M	2	5	-	+	-	+	+	+	4	5	Died

Time from the beginning of illness to hospital admission ranged from 2 to 10 days, but the majority (n=6) on the 3rd to 4th day (median 3.5 days). Patients were evaluated on admission according to the clinical severity score described by Kularatne, SAM et al [11].The median day of commencing TPE was day 5 of illness (range: 3–11 days). In patient 8, the TPE decision was withheld as he didn’t develop significant pulmonary haemorrhages and showed rapid improvement in deranged metabolic parameters.

3.1. Haematological Manifestations and Treatments

Nine patients (90%) exhibited haematological involvement, characterized by thrombocytopenia or a tendency for bleeding, including both non-survivors. Although frequently observed, haematological manifestations seem reversible with intervention provided early, including liberal platelet transfusion to prevent bleeding into vital sites such as the brain and lungs. Patients labelled 3, 4, 6, 8, and 10 received both blood and platelet transfusions. Patient numbers 2 and 5 received blood transfusions only, while Patient number 9 received platelet transfusions only. Out of the two patients who didn’t survive, patient number 10 received both blood and platelets, while patient 9 received only platelets. The patient who didn’t require TPE received both platelet and blood transfusions.

3.2. Renal, Hepatic, Cardiac and Pulmonary Manifestations

Renal impairment was evident in 9 patients (90%) and hepatic dysfunction in six individuals (60%). Renal and hepatic dysfunctions together contributed to severe leptospiral disease and mortality. Two patients who died had both renal and hepatic dysfunction. Seven patients (70%) had myocarditis, including two deceased patients. Poor general conditions were observed in 4 (40%) patients on admission, and only 3 (30%) patients developed pulmonary haemorrhages on admission.

3.3. Clinical Severity Score and Pulmonary Involvement to TPE Decision

Clinical severity scores were evaluated upon admission and at the commencement of TPE. After admission, six more patients developed pulmonary haemorrhage, contributing to a total of nine patients at the onset of TPE, which was deemed the primary reason for the initiation of TPE. Table 3

shows the clinical score at the commencement of TPE. Clinical severity scores, both upon admission and at the commencement of TPE, exhibited a steady trend of deterioration. The average score rose from 3.78 (SD: 0.67) at admission to 4.44 (SD: 0.53) at the time of TPE, with six out of nine patients demonstrating an increase of at least one point, and none showing improvement prior to the intervention. The average duration from admission to TPE was 1.89 days (range: 1–4 days), indicating prompt commencement after clinical deterioration. TPE was generally conducted on Day 5 of illness (median), coinciding with the onset of significant signs such as pulmonary haemorrhage. Among the nine patients who underwent TPE, seven survived, resulting in a survival rate of 77.8%.

Table 3. Clinical Severity score at the beginning of TPE and on admission.

Patient number	Day of illness on admission	Day of Illness At TPE	Severity Score on admission	Severity Score at the beginning of TPE
1-53M	4	6	4	5
2-49F	3	4	3	4
3-57M	5	6	4	4
4-37M	3	4	3	4
5-40M	10	11	3	4
6-44M	3	4	5	5
7-43M	4	8	3	4
8-45M	4	Not done	5	N/A
9-25M	2	3	4	4
10-65M	2	5	4	5

3.4. Description of Fatal Cases

In both fatal cases (Patients 9 and 10), TPE was started on days 3 and 5, respectively—comparatively early in the disease progression. The fatality rate is 22.2%. Nevertheless, both patients exhibited significant multisystem involvement, including myocarditis, at the time of TPE, potentially limiting its therapeutic efficacy. These two patients did not show poor general condition on admission but deteriorated due to the progression of myocarditis-related complications. Both fatalities presented early in the illness (Day 2) and exhibited high severity scores (≥ 4) at both admission and the initiation of TPE. Patient 10, at 65 years, was the oldest in the cohort, suggesting greater physiological vulnerability. Despite timely TPE on Days 3 and 5, both cases advanced quickly, suggesting that in some patients, the progression of disease and host factors, such as age and comorbidities, might decrease the benefit of early intervention.

3.5. Haematological and Biochemical Parameters

Table 4 shows laboratory parameters on admission(A) and at the initiation of TPE (X). Six (60%) patients had haemoglobin (Hb) less than 10 g/dl, and minor variation of Hb% was observed between admission to the commencement of TPE in all patients. As expected, marked thrombocytopenia was found in all patients except cases 2 and 5. However, there is noticeable further drop of platelet count at the beginning of TPE. Leucopenia was not a feature of all patients on admission, and high white cell count persisted at the commencement of TPE, except in case 9, where WBC dropped from 13 to $3.9 \times 10^9/L$.

Severe acute kidney injury was prevalent. Importantly, creatinine levels over 500 $\mu\text{mol/L}$ at the start of TPE did not predict death (for example, Patients 3 and 4 survived), suggesting that kidney injury alone may not lead to poor outcomes if treated promptly and effectively. Patients labelled 2, 3, 4, 5,8 and 10 showed significantly increased AST and ALT levels (>200) at admission. Among them, only patient 10 died:-

Table 4. Comparative Laboratory Parameters on Admission (A) and at Initiation of Therapeutic Plasma Exchange (X).

Patient No	Hb%		Platelet count X 10 ⁹		WBC X 10 ⁹		Creatinine μmol/L		K ⁺ mmol/L		AST U/L		ALT U/L	
	A	X	A	X	A	X	A	X	A	X	A	X	A	X
1	9.5	9.2	39	34	10.9	13.1	213	200	5.1	4.9	39	36	24	22
2	9	9	123	123	9.4	9.4	121	121	3.1	3.1	270	282	132	145
3	8.9	9.5	20	14	9.5	16.3	532	532	5.9	6.1	292	292	152	152
4	12.3	10.1	30	33	10.4	11	606	606	4.3	5	323	323	119	119
5	9.9	7.5	104	89	14.9	17	270	270	5	4	285	296	158	148
6	11.6	10.8	41	24	3.8	3.8	239	239	4.5	4.5	24	24	28.5	28.5
7	12.3	11.4	87	50	18.47	11.9	236	101	3.68	3.8	28.3	39	55	84
8	8.5	n/a	33	n/a	13	n/a	285	n/a	4.2	n/a	260	n/a	106	n/a
9	9	11.1	47	59	13	3.9	108	149	3.4	3.49	21.6	26	24	34
10	11	9.7	30	24	14.08	10.7	303	201	4.7	5.9	425	400	371	342

3.6. Arterial Blood Gas Variation

Arterial blood gas (ABG) at admission and before therapeutic plasma exchange (TPE) was crucial in decision-making (Tables 5 and 6). On admission, most of the patients (n = 9) demonstrated metabolic acidosis characterised by decreased bicarbonate levels and increased lactate concentrations. Also, nine patients were severely hypoxic. Survivors typically demonstrated stable or improved acid-base status and lactate clearance at the time of TPE. In contrast, both non-survivors (9 and 10) exhibited progressive acidemia, with pH decreasing from 7.35 to 7.13 and from 7.2 to 7.1, respectively, with an increase in lactate levels (up to 8.6 mmol/L).

Table 5. Arterial Blood Gas Parameters on Admission (A) and at Initiation of Therapeutic Plasma Exchange (X).

Patient No	pH		pO ₂ mmHg		pCO ₂ mmHg		HCO ₃ mmol/L		Lactate mmol/L	
	A	X	A	X	A	X	A	X	A	X
1	7.34	7.32	75	70	21	23	15.2	17	4.6	2.6
2	7.45	7.45	68	68	37	37	26	26	1.1	1.1
3	7.31	7.3	65	80	35	32	15	19	1.3	2.6
4	7.33	7.412	62	35	33	33	17	17	1.1	1.5
5	7.2	7.2	116	80	29	25	14	14	1.2	1.3
6	6.99	7.24	83.8	131	65.9	44.9	16.1	19.6	3.5	2.2
7	7.34	7.33	74	71	20	22	16	16	1.2	1.3
8	7.34	n/a	40	n/a	39	n/a	21	n/a	5.1	n/a
9	7.35	7.13	51.4	197	25	42	17.9	14.4	2.5	8.6
10	7.2	7.1	89.3	75	15.7	20	7.4	10	2	4.5

Table 6. Blood lactate levels at the commencement of TPE.

	Died	Survived
Blood lactate level at the beginning of TPE (mmol/L)	8.6; 4.5	2.6;1.1; 2.6;1.5; 1.3; 2.2;1.3

3.7. Clinical Score, Outcome Predictors (Tables 7 and 8)

The patients with a clinical score of 3 recovered with TPE. The deceased patients had an initial clinical score of 4. On the contrary, two patients in clinical score 5 survived. Of the nine patients who had plasma exchange, 3 exhibited myocarditis with inotrope dependency at the initiation of TPE, while the remaining 6 either had no myocarditis, no inotrope dependency, or myocarditis without inotrope support. In the subgroup with myocarditis and inotrope dependency, 2 out of 3 patients (66.7%) died, both of whom were receiving three inotropic drugs at the onset of TPE. The only survivor in this group received two inotropes. In contrast, all six patients in the group without inotrope dependency at the initiation of TPE survived, resulting in a 0% mortality rate. The requirement for invasive mechanical ventilation at the commencement of TPE was associated with significantly increased death. In the group of five intubated patients, two died, resulting in a mortality rate of 40% within this category. Conversely, all four non-intubated patients survived, although three necessitated non-invasive ventilatory support (NIV/CPAP). Severe renal involvement required dialysis support for 4 patients, and of them, 1 died and 3 survived. Among the five individuals who did not necessitate dialysis, one died, while four survived. Mortality was high in dialyzed patients (25% vs. 20%), although the limited sample size limits the reliability of the result.

Table 7. Clinical Score category on admission and number of deaths.

Clinical Score on Admission	Number of patients	Number of deaths
3	4	0
4	4	2 (50%)
5	2	0

Table 8. Clinical circumstances and supportive interventions associated with the outcomes in severe leptospirosis patients undergoing TPE.

	Died	Survived
Myocarditis with inotrope dependency at the beginning of TPE	2 (dependent on 3 inotropes)	1 (Dependent on 2 inotropes)
No myocarditis or inotrope dependency or myocarditis without inotrope dependency at the beginning of TPE	0	6
Intubated at the beginning of TPE	2	3
Not intubated at the beginning of TPE	0	4 (NIV/ CPAP-3 patients)
Needed Dialysis during the course of the illness	1	3
Not needed Dialysis during the course of the illness	1	4

NIV: Non-invasive ventilation; CPAP: continuous positive airway pressure.

4. Discussion

In this case series, the duration of the illness was short, and patients were ill with severe metabolic derangement and the therapeutic decision for TPE was taken within a few days after hospital admission. At the presentation, hypoxaemia and metabolic acidosis had set in, that has further deteriorated despite resuscitation. These metabolic derangements were contributed to by multiple organ dysfunctions caused by leptospirosis. Reversing such severe manifestations is a greater challenge even in an ICU setting without highly specific interventions. We found TPE to be a lifesaving procedure for severe leptospirosis, which should be used judiciously. We had a 78% success rate and found inotropic-dependent severe myocarditis, the need for assisted ventilation and dialysis as factors that counter the benefits of TPE. Questions arise as to why TPE failed in two patients who presented to the hospital within 2 days of the onset of illness. Their common features are the development of marked lactic acidosis, hypoxaemia and myocarditis, which require ionotropic support to maintain blood pressure. Probably, myocarditis would have developed early

in these patients, causing them to feel unwell and to seek hospital admission on the 2nd day of illness, but its detection would have been delayed in a busy hospital setting. In a state of cardiac instability, whether TPE may worsen it is another question that needs an answer. All 10 patients were initially given a bolus of methylprednisolone, which has been shown to have a proven benefit in cases of early administration [11]. By convention, the anti-inflammatory action of steroids helps to control myocarditis. So, steroids and TPE together may improve survival rates in severe leptospirosis. The clinical decision regarding the timing of these treatment modalities is essential, as delays are always detrimental.

Therapeutic plasma exchange has many applications in clinical practice [12]. TPE has two distinct ways of action. Clearance of a pathogenic substance from the plasma and administration of substantial quantities of deficient plasma components [12]. Leptospirosis comprises two clinical phases: the septicemic phase and the immune phase. In this latter phase, the body's humoral response functions to eradicate the organism from numerous tissues. Nonetheless, the deposition of immunological complexes during this period could result in endothelial injury [13]. A study conducted by J. Croda et al. indicates that membranous deposits of linear immunoglobulins (IgA, IgG, IgM) and complement on an alveolar surface may precipitate catastrophic pulmonary haemorrhage in leptospirosis in humans [14]. It is reasonable to suppress dysregulated immune responses before the initiation of immunologically mediated tissue destruction.

As leptospirosis is becoming a significant health problem with high mortality, clinicians in southern Sri Lanka use TPE for complicated leptospirosis. They found a promising outcome [10]. Then, clinicians in the rest of Sri Lanka started using TPE. The limiting factor of TPE is the unavailability of the facility in rural farming regions where the disease is common. Our study highlights the value of TPE in the central region of Sri Lanka. Definitely, this knowledge has global application as leptospirosis has a global distribution. This case series, while demonstrating the benefits of TPE, also highlights instances where TPE has failed to provide survival benefits. The cumulative survival rate in this cohort was 78 %; both deceased patients exhibited a clinical severity score of 4 on admission and 4 and 5 at the beginning of TPE, including cardiac and pulmonary involvement. Although the timing of TPE fell within the early treatment window, the degree of systemic involvement likely reduced its effectiveness.

Multiple system involvement is the nature of severe leptospirosis. The factors that contribute to the severity of the disease remain unclear, and the natural cause of the illness remains unpredictable. Therefore, clinical vigilance is essential. Three patients presented with pulmonary haemorrhages at admission, and subsequently, six additional patients experienced pulmonary haemorrhages that required therapeutic plasma exchange (TPE). Seven patients had myocarditis on admission, and three patients necessitated inotropes to sustain blood pressure later in the course of the illness. Both patients who died required intubation due to severe respiratory distress with pulmonary haemorrhages and were diagnosed with myocarditis that needed the use of maximal inotropic support. This pattern suggests that lung haemorrhage and myocarditis are significant factors influencing negative outcomes in leptospirosis, particularly when occurring concurrently. Literature also supports that leptospirosis complicated by both pulmonary haemorrhage and myocarditis has a substantially poor prognosis, particularly in resource-limited settings or when multiple organ systems are implicated [15]. Two deceased patients exhibited a clinical severity score of 4 and 5, indicating significant multiorgan disease at the time of therapeutic plasma exchange (TPE). The behaviour of hepatic transaminases is typical in these cases. Six patients showed considerable hepatic involvement, but fulminant hepatic failure was not a problem. Elevated aspartate transaminase levels serve as a valuable prognostic indicator in advanced leptospirosis [16].

Elevated liver enzymes, particularly in conjunction with renal impairment or thrombocytopenia, may indicate impending organ failure and a worse prognosis. In contrast, stability or early improvement of transaminases appears to be associated with improved survival following TPE. Marked thrombocytopenia was present at admission, and platelet transfusions were needed in severe cases to prevent bleeding.

Hypoxaemia is a cardinal feature in these patients. Also, there was a simultaneous deterioration in acid-base status, indicating ineffective oxygen utilization. Patient 6, presented with severe acidemia (pH 6.99), demonstrated notable improvement following supportive care, underscoring the potential for reversibility through early intervention. We think the presence of worsening acid-base imbalance and hyperlactatemia before therapeutic plasma exchange was linked to unfavorable outcomes. The findings indicate that ABG trends, specifically lactate and bicarbonate dynamics, serve as prognostic markers. The average initial blood lactate concentration in patients who died was markedly elevated compared to that of survivors (6.55 vs. 1.8 mmol/L). All survivors had lactate levels ≤ 2.6 mmol/L, whereas both non-survivors had levels exceeding 4 mmol/L—values typically associated with compromised perfusion and metabolic distress. This suggests that requiring mechanical ventilation due to respiratory failure may be a sign of a worse outcome. In these cases, increased lactate levels likely indicate persistent circulatory shock or significant cellular hypoxia, suggesting that these individuals have advanced to a more severe and less reversible stage of the disease. Furthermore, a Brazilian multicenter retrospective study on 206 leptospirosis patients compared ICU-admitted and non-ICU-admitted patients, revealing that those admitted to the ICU exhibited metabolic acidosis (60.5% vs. 36.5%) and severe metabolic acidosis (11.0% vs. 0%) upon admission. These patients also displayed elevated mortality rates (23.5% compared to 5.7%) [17].

Patients having a clinical grade of 4 showed a markedly higher mortality rate. Two (50%) of the four patients in this category died. Even with therapies like TPE, this score seems to indicate a critical threshold beyond which organ failure and systemic deterioration may accelerate. It's interesting to note that both patients with the highest clinical severity score of five survived. Despite seeming contradictory, this result could be due to a small sample size, the effect of an intensive, multimodal intervention that included timely TPE, or both. These patients likely represent situations where survival depended heavily on early detection, prompt care escalation, and possibly personal physiological resilience.

We observed that the ventilatory state at the beginning of TPE had a significant impact on the outcomes. There were no deaths among patients who were not intubated, including those using non-invasive ventilation (NIV) or CPAP. Still, all documented deaths occurred among patients who were intubated at the start of TPE, with a mortality rate of 40% in this group. This pattern suggests that the need for invasive mechanical ventilation at the beginning of TPE may reflect more advanced disease severity and is associated with worse outcomes. However, the limited sample size precludes statistical significance. These results support the concept that timely TPE commencement may affect survival and highlight the possible benefits of early detection and intervention with TPE—before the development of respiratory failure requiring intubation. To confirm these findings and improve the therapeutic standards for determining the optimal time to administer TPE in the treatment of severe leptospirosis, more research in larger groups is necessary. In a study conducted in Southern Sri Lanka using 88 complicated leptospirosis patients, logistic regression analysis identified intubation and mechanical ventilation as strong independent predictors of mortality, with an odds ratio of approximately 18.5 ($p < 0.001$) [15].

5. Conclusions

In conclusion, the result emphasises the potential advantages of prompt and vigorous therapeutic plasma exchange, even in patients with severe diseases, when performed before the onset of irreversible organ damage. As all these patients initially received methylprednisolone, its benefits are already known [11]. The combination of both treatments could have been complementary in reducing mortality.

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Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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