

# Predictors of Mortality in Severe Leptospirosis

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## ABSTRACT

**Introduction:** Leptospirosis is a widespread zoonosis caused by the spirochete leptospira. Epidemic leptospirosis is being reported from Kerala during the monsoon. Its incidence has increased over the past two decades. Severe leptospirosis results in sepsis with multi organ dysfunction syndrome and mortality rate varies from 5-40%. In this study we attempted to identify the risk factors associated with mortality of leptospirosis.

**Material and methods:** This was a retrospective case-control study among patients diagnosed with severe leptospirosis and admitted in a tertiary care hospital in Thrissur District of Kerala during the monsoon of 2014. Data was collected from case records of 48 patients out of which 21 were cases (non survivors) and 27 were controls (survivors) and Statistical analysis was done using X<sup>2</sup> test with Epi info software.

**Results:** Mean age of study population was 42 yrs. There were 38 male (79%) out of which 14 were cases and 10 females (21%) out of which 7 were cases. Mortality rate was 44%. 77% of them presented with myalgia. Among cases 62% had icterus, 81% had oliguria, 66% underwent mechanical ventilation and 62% undergone blood and blood product transfusion. Dyspnoea (p=0.08), Chest crepitations (p=0.005), decreased urine output (p=0.012), acute kidney injury (p=0.005), hepatic dysfunction (p=0.06), shock (p=0.019), haemoglobin less than 10g% (p=0.03) and platelet count less than 20000 (p=0.025) were found to have significant association with mortality.

**Conclusion:** The severe disease is more common in middle aged males but mortality is more in female. Platelet count less than 20000 and shock were found to be the independent predictors of mortality.

**Key words:** Leptospira, Zoonosis, Weils Disease, Pulmonary Haemorrhage, Acute Respiratory Distress Syndrome, Acute Kidney Injury, Severe Thrombocytopenia, Hepatomegaly, Chest Crepitations

## INTRODUCTION

Leptospirosis is a widespread zoonosis. It is caused by pathogenic spirochetes of the genus *Leptospira*.<sup>1</sup> The disease has a world- wide distribution. It is more common in the tropics because of favourable transmission conditions.<sup>2</sup> Typically the disease occurs as an epidemic in the monsoon season. Usually there will be more than one such epidemic per season. In southern India its incidence has increased over the past two decades. Epidemic leptospirosis is being reported from Kerala during the monsoon months.<sup>3</sup>

The clinical presentation of leptospirosis has a biphasic pattern, with an acute phase (septicaemia) during the first week followed by another one week of immune phase which is characterized by the production of antibody and excretion of leptospira in urine. Severe disease is seen in 5–15% of all

human infections.<sup>1</sup> Most of the complications of the disease occurs during the immune phase because of localization of leptospira in the body tissue. This usually happens in two weeks from disease onset.<sup>4</sup>

Severe leptospirosis results in sepsis with multiple organ dysfunction syndrome. The pathogenesis and clinical manifestations of leptospirosis are distinct from other bacterial infections. Unlike other infections like dengue which causes widespread systemic manifestations leptospirosis causes very specific organ damage to the liver, kidneys, central nervous system and heart.<sup>5</sup> Weil's disease, a severe form of leptospirosis, is characterized by jaundice, haemorrhage and renal failure.<sup>1</sup> With proper supportive treatment even in severe infections recovery is possible but still the mortality rate varies from 5% to 40%.

We attempted to identify the risk factors associated with mortality in patients having severe leptospirosis during an epidemic of leptospirosis in the year 2014. We used retrospective case control model for the study because it could be completed in a short time period, the data obtained will be conclusive and as the outcomes has already occurred the ethical problems involved could be minimised as the disease is a lethal one. As the study includes multiple variables this model was found to be a convenient one. The comparison of variables of survivors and non survivors could reveal the factors associated with mortality.

Most of the earlier studies shows severe disease is predominant in males. Hepatitis like early complications orders caution in the primary care setting. Assessing lung and central nervous system involvement is significant as a predictor of lethal outcome.<sup>3</sup> Leptospirosis associated with acute kidney injury has 22% mortality.<sup>6</sup> The severe pulmonary haemorrhage syndrome (SPHS) in leptospirosis has case fatality higher than 50% in many reports.<sup>3</sup> In case of severe leptospirosis pulmonary involvement at the time of admission is a strong predictor of mortality.<sup>7</sup>

Epidemic of leptospirosis has become a major urban health problem, associated with high mortality. The leptospirosis has different clinical presentation in different geographic areas. The mortality is increasing in Kerala.<sup>8</sup> Diagnostic

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confusion with dengue fever and other emerging infectious disease with a similar geographic distribution prevent timely intervention that could minimise mortality. Clinical presentation of leptospirosis is needed to be studied to enhance its recognition and appropriate early treatment. Predictors of lethal outcome and prognostic factors must be evaluated. In Thrissur District of Kerala a study on this subject is essential because leptospirosis is endemic in this area and it rise to epidemics in monsoon season with significant mortality.<sup>3</sup> Further clinical and epidemiological studies are necessary to determine the total burden of illness in the community.

## MATERIAL AND METHODS

A retrospective case-control study was planned. Ethical clearance was obtained from institutional research committee. In-patient number of all cases diagnosed as severe leptospirosis and admitted in the year 2014 was collected from the Intensive Care Unit register. Written permission was taken through proper channel from the superintendent of the hospital and head of general medicine department to collect case records from the records library. Data was collected from these case records in a proforma and entered into excel sheet and analysed. Study site was a tertiary care hospital in Thrissur, District of Kerala and the duration was of 2 months (June 2014 – July 2014.)

All the patients admitted in the study site (during the months of June and July 2014) and diagnosed to have severe leptospirosis were included in the study. Total number of subjects in the study was 48 out of which 21 were non survivors and 27 were survivors. Cases were defined as patients who died of severe leptospirosis and Controls were the patients diagnosed of severe leptospirosis and have survived.

Cases were included if the cause of death during hospitalization was directly attributable to complications of leptospirosis. Data collection protocol include review of medical records, with description of demographic, epidemiologic, clinical, and laboratory information of lethal cases and survivors who had been hospitalized. Name, age, sex, address, clinical examination findings, vitals, past history, clinical history, epidemiological history, investigations, urine output, complications and management were recorded and analysed. Laboratory confirmation results taken were enzyme-linked immune sorbent assay (ELISA), immunoglobulin M (IgM), microscopic agglutination test (MAT) or PCR. Laboratory values analysed were from the time of admission.

Severe disease is defined by requirement for admission in intensive care unit, acute kidney injury and/or pulmonary involvement. Oliguria is defined as urine output less than 400 mL/day. Pulmonary involvement included dyspnea, haemoptysis, pulmonary rales on physical examination, and intubation.

## STATISTICAL ANALYSIS

Epi info was used for analysis after entering data in Excel sheet. Comparison between qualitative variables was done using the  $\chi^2$  test. The relationship between cases and controls were evaluated using logistic regression, with the dependent variable being death. Variables for multivariate analysis were chosen from significant findings from the univariate analysis.

## RESULTS

**Descriptive analysis:** All together 48 case records were studied. In that 38 were men (79%) and 10 were women (21%). Out of this 21 were non survivors (cases) and 27

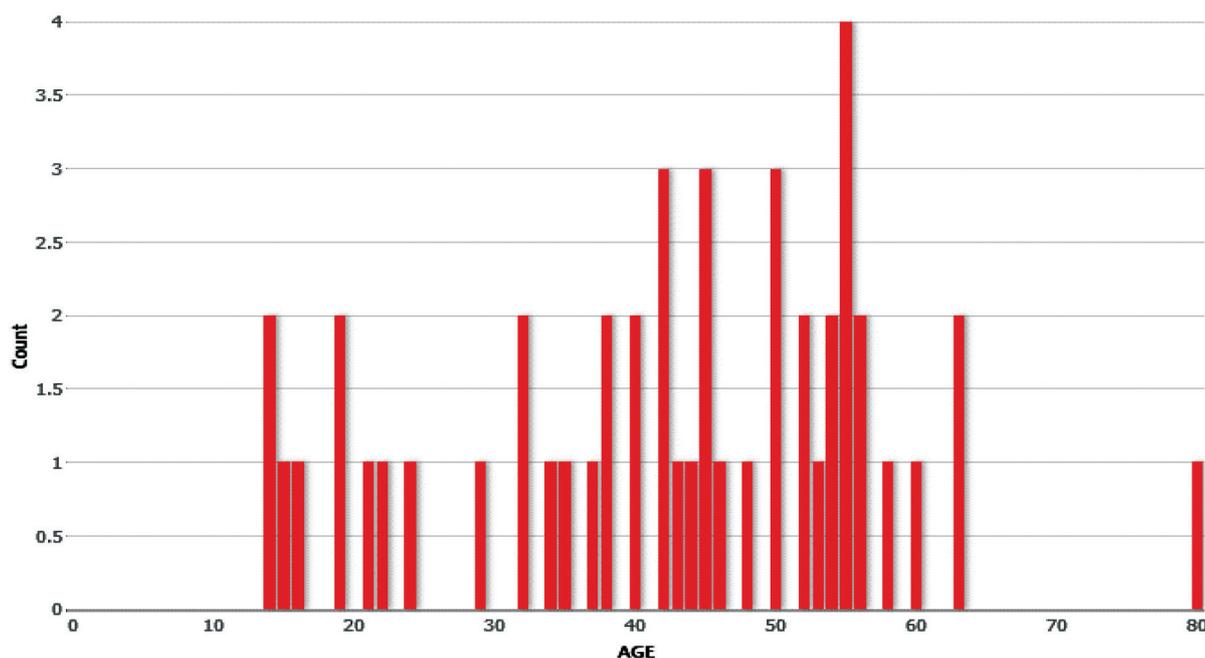


Figure-1: Graph showing age distribution in study

	Cases (n=21)	%	Controls (n=27)	%	Total	Total percent- age	P value
Fever	21	100.00	27	100.00	48	100	1
Head ache	4	19.05	11	40.74	15	31.25	0.19
Muscle pain	15	71.43	22	81.48	37	77.08	0.63
Decreased urine output	17	80.95	11	40.74	28	58.33	0.012
Altered sensorium	7	33.33	4	14.81	11	22.91	0.24
Loose stools	5	23.81	6	22.22	11	22.91	0.82
Cough with expectoration	6	28.57	5	18.52	11	22.91	0.63
Dyspnoea	14	66.67	10	37.04	24	50	0.08
High coloured urine	7	33.33	14	51.85	21	43.75	0.32
Hemoptysis	2	9.52	1	3.70	3	6.25	0.82
H/o diabetes mellitus	3	14.29	3	11.11	6	12.5	0.91
H/o hypertension	4	19.05	3	11.11	7	14.58	0.71
H/o renal disease	3	14.29	1	3.70	4	8.33	0.42
H/o chronic liverv disease	2	9.52	3	11.11	5	10.41	0.76
H/o copd	4	19.05	1	3.70	5	10.41	0.21
H/o smoking	6	28.57	8	29.63	14	29.16	0.81
H/o alcohol consumption	8	38.10	10	37.04	18	37.5	0.82
Pallor	8	38.10	4	14.81	12	25	0.13
Icterus	13	61.90	15	55.56	28	58.33	0.88
Cyanosis	2	9.52	0	0.00	2	4.17	0.36
Pedal edema	10	47.62	6	22.22	16	33.33	0.12
Conjunctival suffusion	7	33.33	15	55.56	22	45.83	0.21
Purpura	2	9.52	0	0.00	2	4.17	0.36
Splenomegaly	2	9.52	2	7.41	4	8.33	0.79
Hepatomegaly	8	38.10	8	29.63	16	33.33	0.96
Chest crepitations	13	61.90	5	18.52	18	37.5	0.005
Rhonchi	4	19.05	0	0.00	4	8.33	0.065
Pulse>100	12	57.14	8	29.63	20	41.66	0.1
Hypotension	6	28.57	4	14.81	10	20.83	0.42
Hemoglobin<10g%	11	52.38	5	18.52	16	33.33	0.03
Total count>11000	9	42.86	7	25.93	16	33.33	0.86
Platele count<20000	8	38.10	2	7.41	10	20.83	0.025
Urine albumin present	10	47.62	13	48.15	23	47.91	0.79
Total bilirubin>10	5	23.81	4	14.81	9	18.75	0.67
Blood urea>40	19	90.48	18	66.67	37	77.08	0.1
Hyperkalemia	4	19.05	1	3.70	5	10.41	0.21
Rbs>200	5	23.81	6	22.22	11	22.91	0.82
Aki	13	61.90	5	18.52	18	37.5	0.005
Hepatic dysfunction	11	52.38	5	18.52	16	33.33	0.06
Ards	20	95.24	5	18.52	25	52.08	0.0000017
Shock	7	33.33	1	3.70	8	16.66	0.019
Coagulopathy	1	4.76	0	0.00	1	2.08	0.89
Haemodialysis	4	19.05	2	7.41	6	12.5	0.44
Peritoneal dialysis	2	9.52	1	3.70	3	6.25	0.82
Mechanical ventilation	14	66.67	1	3.70	15	31.25	0.00014
Blood/ blood products transfusion	13	61.90	3	11.11	16	33.33	0.0006

**Table-1:** Showing variable distribution among cases, controls and total population

were survivors (controls). Among the non survivors 7 were women and 14 were men. The mean age of total subjects were 42.33 with a standard deviation of 15. The age distribution is shown in figure 1. There were 2 cases from outside kerala,

26 from Thrissur District, 16 from Palakkad District, 2 from Malapuram District. Average days of hospitalisation was found to be 3.75 in which the the survivors have an average of 5 days and non survivors had an average of 2.25 days.

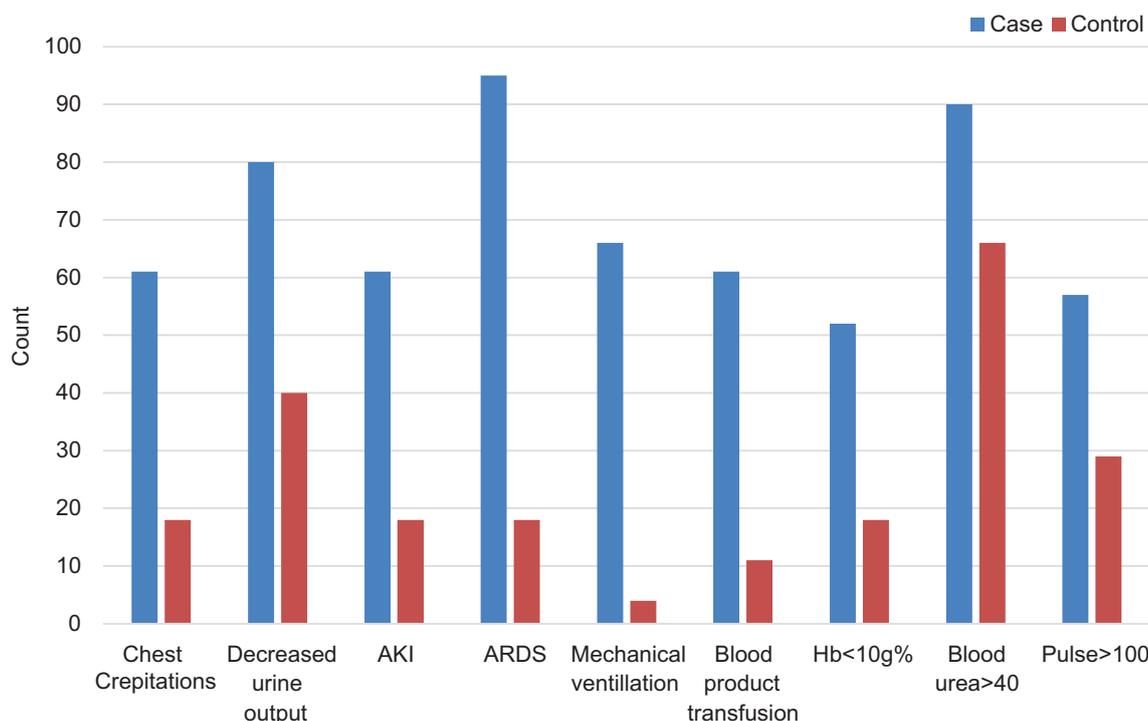


Figure-2: Showing percentage of significant factors among cases and controls

	Odds ratio	95% CI	X <sup>2</sup> corrected	Corrected 2 tailed P
ARDS	88	9.45-819.07	24.86	0.0000017
Mechanical ventilation	52	5.79-466	18.9	0.000014
Shock	13	1.44-116.5	5.48	0.019
Blood and blood product transfusion	13	2.93-57.6	11.52	0.00068
Platelet count<20000	7.69	1.42-41.6	5.01	0.025
Creptitation	9.34	1.92-26.5	9.48	0.002
AKI	7.15	1.92-26.5	7.72	0.005
Decreased urine output	6.18	1.63-23.4	6.29	0.012
Hepatic dysfunction	4.8	1.32-17.6	4.6	0.03
Dyspnoea	3.4	1.02-11.25	3.0	0.08
Hb<10g%	4.84	1.32-17.6	4.66	0.03

Table-2: Showing factors associated with mortality with corresponding odds ratio

Term	Odds Ratio	95% Confidence interval		coefficient	Z-Statistic	P-value
Acute kidney injury	3.88	0.35	42.69	1.35	1.11	0.26
Chest crepitations	2.82	0.31	25.01	1.03	0.93	0.35
Decreased urine out put	10.71	0.79	143.86	2.37	1.78	0.07
Dyspnoea	1.52	0.15	15.18	0.42	0.36	0.71
Haemoglobin <10g%	4.10	0.46	36.34	1.41	1.26	0.20
Hepatic dysfunction	1.38	0.13	14.5	0.32	0.27	0.78
Platelet count	29.84	1.43	619.52	3.39	2.19	0.02
Shock	32.61	1.00	1109.95	3.48	1.93	0.05
constant	*	*	*	-4.65	-3.21	0.0013

Table-3: Binomial logistic regression with dependent variable being death.

**Univariate analysis:** All the patients were presented with fever. Variables distribution among cases, controls and total population with their statistical significance is shown in table 1. Among the total subjects (48) more than 75% had fever (100%), myalgia (77%) and an increased blood urea level more than 40mg/dl (75%) and less than 20% were suffering from co morbidities (Diabetes mellitus, hypertension, renal

disease or liver disease). Average heart rate was found to be 100.58. All were treated with intra venous antibiotics mainly crystalline penicillin. More than 50% of the patients had Icterus (58%), decreased urine output (58%) and acute respiratory distress syndrome (52%). Interventions like mechanical ventilation were given to 31% of patients and blood or blood product transfusion to 33% of patients.

A major disparity among cases and controls were seen in chest crepitations (61% of cases but 18% of controls), acute kidney injury (61% of cases but 18% of controls), acute respiratory distress syndrome (95% of the cases but 18% of controls), Mechanical ventilation (66% of cases but 4% of controls) blood or blood product transfusion (61% of cases and 11% of controls) (fig-2).

On analysing the data it is found that 11 variables are statistically significant in this study. Factors associated with death which were found statistically relevant were chest crepitations with OR(odds ratio) 7.15(1.92-26.5), dyspnoea with OR 3.4(1.02-11.25), decreased urine output with OR 6.18, decreased platelet count (below 20 thousand) with OR 7.69(1.42-41.6), hepatic dysfunction with OR 4.8(1.63-23.4), shock with OR 13(1.44-116.5), acute kidney injury with OR 7.15(1.92-26.5), acute respiratory distress syndrome with OR 88(9.45-819.07), blood and blood product transfusion with OR 13(2.93-57.6), Haemoglobin less than 10g% with OR 4.84 (1.32-17.6) and mechanical ventilation with OR 52(5.79-466) (table 2).

**Multivariate analysis-Logistic Regression:** On multivariate analysis, done through logistic regression platelet count less than 20000 with OR 29.84 (1.43-619.5) and shock with OR 32.6 (1-1109.9) were found out to be independent risk factors associated with mortality. Decreased urine output also shows significance but it is in the brim with an OR 10.71(0.79-143.86) (table 3).

## DISCUSSION

This was an unmatched case control study. There were 48 patients included out of which 21 were cases and 27 were controls. It is found that the severe disease is common in middle aged men than women. The percentage of male is more than female in most of the reports. A similar study in Kerala had 60% men in study population while it was 94% in a study from Thailand.<sup>3,10</sup> In our study the percentage of men was 79%.

The mean age in this study is 42. The mean age ranged from 35 to 50 in other studies.<sup>3,10,14</sup> The mortality rate in this study is 44%. But in previous studies from Kerala and Thailand it was 6.03% and 1.4% respectively.<sup>3,10</sup> In Brazil it had gone up to 15%.<sup>1</sup> May be this disparity was due to inclusion criterion or small sample size.

All the patients were presented with fever. 77 % of them had myalgia. The majority of cases had classical Weil syndrome and multi system involvement. On univariate analysis factors like acute kidney injury, acute respiratory distress syndrome, chest crepitations, decreased urine output, dyspnoea, haemoglobin <10g%, hepatic dysfunction, mechanical ventilation, platelet count <20000, shock and blood product transfusion were found significantly associated with death. Hepatic dysfunction with OR 4.8 (1.32-17.6), decreased haemoglobin level (<10g %) with OR 4.8 (1.32-17.6) and dyspnoea with OR 3.4(1.02-11.25) were better predictors because of the comparatively small class interval. Even though some factors like acute respiratory distress syndrome (OR 88), mechanical ventilation (OR 52) and shock (OR 13)

showed greater association with mortality their significance could not be confirmed because of inflated values and bigger class interval. This may be happened because of small sample size. This problem was faced also during multivariate analysis.

Other factors like acute kidney injury (OR 7.15), chest crepitations (OR 9.34), decreased urine output (OR 6.18), platelet count <20000 (OR 7.6) and blood product transfusion (OR 13) were also found statistically significant in predicting mortality.

But in multivariate analysis only platelet count less than 20000 and shock were found out to be independent predictors of mortality. Thrombocytopenia was observed in 65% cases in an earlier study in Kerala.<sup>3</sup> A study in Brazil it was found to be predictor of mortality with odds ratio 2.6.<sup>1</sup>

Most of the recent studies say pulmonary involvement is a very good predictor of mortality. Pappachan et al identified pulmonary involvement as a predictor of mortality with an odds ratio 5.32. Studies conducted in Brazil, Mumbai and Thailand also reported pulmonary involvement as a mortality predictor.<sup>1,10,18</sup> In this study also pulmonary symptoms and signs were seen in majority of patients. In univariate analysis chest crepitations and acute respiratory distress syndrome were found significant with odds ratio 9.34 and 88 respectively.

The study has many limitations. The small sample size was an important one. This was the cause for the inflated values in statistical analysis. The time limit was another limitation faced. Because only a single person was investigating blinding techniques could not be implemented. This may have caused unnoticed bias.

## CONCLUSION

Within the limitations of the study it is found out that chest crepitations, dyspnoea, decreased urine output, decreased platelet count (below 20 thousand), hepatic dysfunction, shock, acute kidney injury, acute respiratory distress syndrome, blood and blood product transfusion, Haemoglobin less than 10g% and mechanical ventilation were factors associated with mortality. In this Platelet count less than 20000 with an adjusted OR 29.84 and shock with an adjusted OR 32.6 are the independent predictors of mortality. It is also found that severe disease is common in males in the age group 40-50.

Certain factors were found to have high association with mortality in this study but on statistical analysis they produce inflated values. So the significance of these variables could not be confirmed. This was caused due to small sample size. If another study conducted with a larger sample size could help in confirming the significance of these factors in mortality.

A much elaborate study on this topic will help to develop a predictor formula for chance of dying due to leptospirosis. That would be very helpful in better management of the patient from the time of admission itself.

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