Prognostic Factors Associated with Severe Leptospirosis

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Abstract

To determine the prognostic factors associated with severity and death of leptospirosis, the authors conducted a hospital based cross sectional study by collecting data of adult patients that were admitted to Phrae Hospital for leptospirosis from 1998 to 2001. The serology was confirmed with a microscopic agglutination test (MAT). The variables obtained from the history, examination, behavioral risks, investigations, and initial treatment especially the data of the first day of admission were examined for association with severity. Of 362 patients, 214 were classed as nonsevere patients, 81 were severe with complications (serum creatinine $\geq$ 3 mg/dl and/or patients with respiratory failure) and 67 died. Multivariate logistic regression demonstrated that five factors were independently associated with severity : hemoptysis, platelet count (Plt) < 100,000/mm^3, total bilirubin > 2.5 mg/dl, white blood cell count > 13,000/mm^3 and hematocrit (Hct) < 30 per cent. Five factors associated with mortality are : respiratory failure (or respiratory rate; RR > 24/min), hemoptysis, oliguria, metabolic acidosis (or bicarbonate < 20mmol/l) and thrombocytopenia (or Plt < 100,000/mm^3). Identification of these factors might provide useful selection criteria for patients who need early admission or transfer to the intensive care unit

Key word : Severe Leptospirosis, Mortality, Acute Renal Failure, Respiratory Failure

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Leptospirosis is a common zoonotic disease in the tropics, characterized by great clinical variability ranging from mild flu-like illness to severe multisystem and life threatening condition[1,2]. A number of risk factors that contribute to mortality have been identified in previous studies such as advanced age, altered mental status, renal insufficiency (ARF), presence of oliguria, dyspnea, pulmonary hemorrhage (PH), respiratory insufficiency, or leukocytosis[3-8]. Some variables were referred to be associated with severe leptospirosis by univariate analysis, such as thrombocytopenia, anemia, hypotension and hyperbirilubinemia[9-14].

In the present study, the authors analyzed the data at admission to find the impact of multiple clinical factors upon the mortality or severity of patients with leptospirosis admitted to our hospital during an outbreak of leptospirosis in Phrae Province of Thailand. By identification of these prognostic factors, the authors can predict the severe forms of leptospirosis at the time of admission. The early evaluation of disease severity might be useful in improving the care of patients with leptospirosis.

METHOD

Patient population

This study was performed in Phrae Hospital, a 430-bed hospital with a 16 bed intensive care unit for adult patients in the northern part of Thailand. All patients with serological diagnosis of leptospirosis, during an outbreak of leptospirosis in Phrae Province in the year 1998-2001, were retrospectively included in the study. Leptospirosis was diagnosed in accordance with World Health Organization (WHO) criteria, confirmed by leptodipstick or immunofluorescent antibody (IFA) and a microscopic agglutination test (MAT) was performed to identify the serotypes. The 67 fatal patients had high WHO scores ($\geq$ 26), presented during an outbreak of disease but could not correct the second serum specimen for serological confirmation because death occurred early in the course of the disease. The patients were treated with intravenous penicillin (1.5 million unit every 6 hours[15], combined with third generation cephalosporin in some cases).

Clinical definition

Severe leptospirosis is defined as a serological confirmed leptospirosis patient with serum creatinine $\geq$ 3 mg/dl and /or with respiratory failure, oliguria (urine output < 0.4 L/24 h), jaundice (total bilirubin > 2.5 mg/dl), dyspnea (respiratory rate > 24/min), hypotension (systolic arterial pressure < 90 mm Hg), thrombocytopenia (platelet count < 100,000/mm^3).

Study design

The study was a hospital based cross sectional study of 362 patients in Phrae Hospital. The patients were classified into three groups : 214 nonsevere patients (group one), 81 severe patients (group two) and 67 fatal patients (group three).

Statistical method

Results are expressed as means $\pm$ SD or as percentages. A multiple stepwise logistic regression was applied to the data to determine the association between risk factors and mortality or severity of leptospirosis patients (SPSS software for window; SPSS, Chicago). The authors first compared the variables between the 67 fatal patients with the 295 survivors, then we compared between the 214 nonsevere patients and the 81severe patients. A value of $p < 0.05$ was considered significant. Sensitivity and specificity of the logistic regression equation were estimated.

RESULT

362 patients met the inclusion criteria, including 214 nonsevere patients,81 severe patients and 67 fatal patients. 295 survivors had the two serum sample corrected with one serum sample of titer above 1 : 400 or four fold rising of titers. The common serotypes were *L. pyrogenes* (1998), *L. pyrogenes* and *L. bratislava* (1999), *L. bratislava* (2000-2001). The other serotypes were *L. akaiyami, L. rachmati, L. saigon, L. pomona, L. ballico, L. javanica, L. wolfii, L. icterohaemorhagiae, L. hebomadis, L. canicola* and *L. copenhageni.*

Most of the patients were farmers and fishermen. Of the three groups, mean age did not differ. Fatal and severe cases had a slightly delayed duration of symptoms ($p > 0.05$). 76.6 per cent were male, presented with fever (99.2%), headache (74.1%), myalgia (89.3%), calf muscle tenderness (45.2%), high fever above 39°C (43.2%), conjunctival suffusion (56.2%), mild proteinuria with red blood cells and white blood cells (61.4%), nausea or vomiting (36.1%), abdominal pain (17.4%), diarrhea (14.3%), hepatomegaly (42.1%), and chill (30%). The percentage of patients with jaundice, hemoptysis, oliguria, respiratory failure, peritoneal dialysis, dyspnea, and abnormal lung infiltration increased from group one to group three. The mean respiratory rate (RR), white blood cell count (WBC),

serum creatinine (Cr), and total bilirubin (TB) increased from group one to group three. The mean hematocrit (Hct), platelet count (Plt), serum bicarbonate (HCO3) decreased from group one to group three. The percentage of polymorphoneuclear cell (PMN%), serum sodium (Na), serum potassium (K), serum chloride (Cl), serum transminase, and serum alkaline phosphatase did not differ. (Table 1)

With the final model, the authors identified five significant independent variables ($p < 0.05$) associated with mortality of 97.3 per cent sensitivity and 86.6 per cent specificity, including respiratory failure, hemoptysis, oliguria, metabolic acidosis and thrombocytopenia (Table 2). If we used "dyspnea (RR > 24/min)" instead of "respiratory failure" and used a simple cut-off point, it was found that the five significant independent variables associated with mortality were RR > 24/min, hemoptysis, oliguria, HCO3 < 20 mmol/l, and thrombocytopenia (Plt < 100,000/mm^3) (Table 3).

The authors also identified five significant independent variables (Table 4) associated with the severity of leptospirosis of 90.7 per cent sensitivity and 65 per cent specificity. The variables included in the statistical analysis were simple variables that were derived from history, physical examination, and complete blood count (CBC). The authors used the cut-off point of total bilirubin at 2.5 mg/dl for jaundice because it was easy to detect from a physical examination. The prognostic factors were hemoptysis, thrombocytopenia (Plt < 100,000/mm^3), jaundice (TB > 2.5 mg%), leukocytosis (WBC > 13,000/mm^3), and anemia (Hct < 30%). If the authors combined the fatal cases (all were severe cases) with severe group, the five factors were the same and "RR > 24/min" was also prognosticaly significant, with 86.8 per cent sensitivity and 77.1 per cent specificity.

DISCUSSION

The mortality rate of leptospirosis varies from 5 per cent-22 per cent according to the different criteria for patient inclusion[3-6,11,12]. Compared with these previous reports, the prognostic factors associated with mortality were similar to the data in the

Table 1. Characteristics of cases.

	Nonsevere (n = 214) (Mean ± SD)	%	Severe (n = 81) (Mean ± SD)	%	Death (n = 67) (Mean ± SD)	%
Age (yrs)	38.50 ± 12.46		41.96 ± 13.60		41.07 ± 14.65	
Length of symptom(d)*+#	3.66 ± 3.03		4.65 ± 1.83		4.66 ± 2.12	
Length of stay(d)*+#	4.34 ± 1.96		9.58 ± 5.68		3.24 ± 4.26	
Respiratory rate (/min)*+#	21.65 ± 4.40		23.09 ± 3.83		27.71 ± 6.88	
Pulse rate (/min)*+#	93.29 ± 14.77		98.53 ± 16.23		107.6 ± 18.84	
White blood cells (*1,000/mm^3)*+#	9.77 ± 4.22		13.3 ± 5.48		14.59 ± 9.24	
%PMN (Neutrophil)*	84.39 ± 9.41		85.75 ± 8.21		87.61 ± 6.14	
Hematocrit (%)*+#	37.37 ± 5.80		32.85 ± 6.50		32.67 ± 6.04	
Platelet count (*1,000/mm^3)*+#	157.14 ± 94.06		69.39 ± 67.45		48.56 ± 64.51	
Urea nitrogen (mg/dl)*+#	17.66 ± 10.89		73.23 ± 45.36		62.31 ± 36.74	
Creatinine (mg/dl)*+#	1.12 ± 0.48		4.56 ± 2.08		3.87 ± 2.15	
Bicarbonate (mmol/dl)*+#	23.44 ± 2.75		20.46 ± 3.00		18.83 ± 4.79	
Total bilirubin (mg/dl)*+#	1.84 ± 2.97		8.96 ± 8.72		7.36 ± 9.79	
Asparate aminotransferase (mg/dl)*+#	58.22 ± 53.2		74.94 ± 66.25		141.91 ± 202.85	
Alanine aminotransferase (mg/dl)	54.53 ± 49.65		54.38 ± 39.63		84.67 ± 109.61	
Hypotension*+	46	21.4	36	44.4	24	35.8
Hemoptysis*+#	7	3.3	10	12.5	15	22.4
Oliguria*+#	0	0	20	24.7	40	59.7
Respiratory failure*+#	0	0	9	11.1	58	86.6
PD (peritoneal dialysis)*+#	0	0	26	32.1	41	61.2
Total bilirubin > 2.5mg/dl*+#	35	16.4	59	72.8	42	62.7
Respiratory rate > 24/min*+#	8	3.8	2	14.8	38	57.6
Infiltrates on chest radiograph	8	3.7	24	29.6	34	50.7

* $p < 0.05$, Compare between nonsevere with severe (included death).
+ $p < 0.05$, Compare between nonsevere with severe.
# $p < 0.05$, Compare between nonsevere and severe (survivor) with death.

Table 2. Prognostic factors for death (compared between survivors and nonsurvivors).

Risk factors	B	Sig.	OR	95% CI	
				Lower	Upper
Respiratory failure	4.757	0.000	116.4	36.3	373.2
Hemoptysis	1.752	0.014	5.8	1.4	23.3
Oliguria	1.493	0.009	4.5	1.5	13.7
Serum bicarbonate	-0.265	0.002	0.767	0.650	0.905
Platelet count	-0.010	0.006	0.990	0.983	0.997
Constant	2.338				

Coefficient (B), p-value (Sig), Odd ratio (OR), Confidence interval (CI)

Table 3. Prognostic factors for death (comparison between survivors and nonsurvivors).

Risk factors	B	Sig.	OR	95% CI	
				Lower	Upper
Hemoptysis	1.169	0.032	3.2	1.1	9.4
Respiratory rate > 24/min	2.090	0.000	8.1	3.6	18.1
Oliguria	1.992	0.000	7.3	3.2	16.7
Serum bicarbonate < 20mmol/l	1.025	0.011	2.8	1.3	6.1
Platelet count < 100,000/mm^3	1.507	0.005	4.5	1.6	12.9
Constant	-4.141				

Table 4. Prognostic factors for severity (comparison between nonsevere and severe cases).

Risk factors	B	Sig.	OR	95% CI	
				Lower	Upper
Hemoptysis	1.585	0.015	4.9	1.4	17.6
Platelet < 100,000/mm^3	1.960	0.000	7.1	3.4	14.9
TB > 2.5 mg/dl	1.968	0.000	7.2	3.6	14.3
WBC > 13,000/mm^3	1.038	0.006	2.8	1.4	5.9
Hematocrit < 30%	1.069	0.016	2.9	1.2	6.9
Constant	-3.611				

present report, but the studies that compared between survivors and nonsurvivors failed to demonstrate some differences, as in the present report, because they compared the severe group and nonsurvivors group that were almost the same group of patients such as in the report by Albert IKO (91% of patients were icteric)[6] and Dupont (85.3% icteric)[4]. When the authors recruited the nonsevere patients, many different factors that can predict the severity of disease at the time of admission were demonstrated.

Most of the fatal cases died within the first five days of admission and there was a slight delay in duration of symptoms before admission with no statistical significance. The causes of death were oliguric ARF and/or PH or respiratory insufficiency. The authors also found a high prevalence of hypotension during the first twenty four hours after admission (Table 1) as other reports from Thailand[12,13] and this was probably associated with the high incidence of oliguric ARF in the present report, supposing that these patients had hypotension sometime before admission, then oliguria occurred early on admission and was associated with mortality. Niwattayakul K et al[12] reported that hypotensive patients were more severe and associated with acute renal failure and/or PH. Hypotension in leptospirosis can be caused by hypovolemia and decreased systemic vascular resistance induced by vasodilating cytokines and mediators [12,16-18]. With prompt attention and treatment, hypotension during the first twenty four hours after admis-

sion was not associated with mortality or severity in the present report.

When compared with the prognostic factors associated with mortality in ARF[19], many factors were the same, because in severe cases of leptospirosis the patients also had a high incidence of ARF. The factor that was found to be associated specifically with leptospirosis (both mortality and severity) was thrombocytopenia, the lower the platelet count, the higher the severity. The data supported the theory of vasculitis or endothelial cell damage from leptospire's toxin which caused the pathology both in the kidneys [16] and lungs[20], and induced the platelet consumption during leptospiremic phase. Higgin and Cousineau demonstrated a drastic reduction of the platelet count from day 1-5 following intraperitoneal injections of leptospires[21]. Edwards CN and Raoult D demonstrated the association of thrombocytopenia and ARF by univariate analysis, the platelet decreased from day 5-7[9,10]. There was no clinical, laboratory or histopathologic evidence of the disseminated intravascular coagulation (DIC) in leptospirosis[20,22] and thrombocytopenia was not associated with DIC. The incidence of thrombocytopenia varied from 18 per cent-78 per cent in many reports[23-26] because of the different inclusion criteria.

Confirming the previous report[4-6], jaundice was not the risk factors for mortality in the present report. Icteric patients had a higher severity and higher risk of ARF[14] but the mortality was not from hepatic failure. The patients died from another complications of the disease.

Pulmonary manifestations are frequently observed in patients with leptospirosis. Such abnormalities have been reported in 20-70 per cent of patients in several studies[27]. The common symptoms are cough, hemoptysis and chest pain. Dyspnea, PH, abnormal alveolar infiltration from chest radiography or respiratory failure are related to mortality of the disease[3,4,6,28]. In the present report it was found that hemoptysis was an important clinical symptom to observe. It indicated a high risk of severe pulmonary complication or death.

Bicarbonate wasting was an important process for metabolic acidosis in leptospirosis[29]. The process of sepsis and ARF made metabolic acidosis more pronounced. In the present report the presence of metabolic acidosis ($HCO3 < 20$ mmol/l) was related with both severity (data not shown) and mortality.

A high incidence of anemia was found in severe leptospirosis and dead cases. This is related to severity probably because endothelial cell damage and occult hemorrhage occurred especially from lung pathology. The study by Park S et al (Chonbuk, Korea) in 1987 found a high incidence of anemia and thrombocytopenia in patients who had PH[11]. The study of Albert IKO from Brazil[6] in which severe cases were recruited, also found a high incidence of anemia.

In summary, related to the management of patients with leptospirosis, after making a clinical diagnosis from WHO criteria, these prognostic factors can help in diagnosis and in decision making, whether to admit the patients in the ward or the ICU. With early patient management, including intravenous penicillin administration and close monitoring of those at high risk of severity or mortality, the outcome of leptospirosis treatment can be improved.

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ปัจจัยที่สัมพันธ์กับโรคเลปโตสไปโรสิสที่มีอาการรุนแรง

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เลปโตสไปโรสิส มีลักษณะการแสดงของโรคแตกต่างกันได้มาก ตั้งแต่อาการน้อย จนกระทั่งรุนแรงและเสี่ยงต่อการเสียชีวิต การประเมินความรุนแรงของโรคจะมีประโยชน์ต่อการตัดสินใจพิจารณาให้การดูแลรักษาผู้ป่วย เพื่อประเมินปัจจัยเสี่ยงที่มีผลต่อความรุนแรงของโรค และปัจจัยเสี่ยงที่เสี่ยงต่อการเสียชีวิตของผู้ป่วย คณะผู้วิจัยได้ทำการศึกษา Hospital based cross sectional study ในผู้ป่วยที่ได้รับการวินิจฉัยว่าป่วยด้วยโรคเลปโตสไปโรสิส ที่รับไว้รักษาตัวที่โรงพยาบาลแพร่ ตั้งแต่ พ.ศ. 2541–2544 ผลการตรวจยืนยันด้วยวิธี microscopic agglutination test (MAT) ตัวแปรที่ใช้วัดเป็นข้อมูลทั่วไปของผู้ป่วย ข้อมูลการป่วย อาการ อาการแสดง พฤติกรรมเสี่ยงต่อการเกิดโรค และข้อมูลการตรวจชันสูตรเพิ่มเติม ผู้ป่วยที่นำเข้าศึกษา 362 ราย แยกเป็น 3 กลุ่ม คือกลุ่มอาการไม่รุนแรง 214 ราย กลุ่มที่มีความรุนแรงของโรคสูง (ระดับซีรัม creatinine $\geq$ 3 mg/dl และ/หรือ มีภาวะ respiratory failure) (87ราย) และกลุ่มที่เสียชีวิต (67ราย) วิเคราะห์ความสัมพันธ์ระหว่างปัจจัยกับความรุนแรงของโรคและการเสียชีวิตด้วย multiple logistic regression พบว่าปัจจัยที่มีผลต่อความรุนแรงของโรค คือ hemoptysis, platelet count (Plt) < 100,000/mm^3, total bilirubin > 2.5 mg/dl, white blood cell count > 13,000/mm^3 และ hematocrit (Hct) < 30% ส่วนปัจจัยที่เสี่ยงต่อการเสียชีวิต คือ respiratory failure (หรือ respiratory rate; RR > 24/min), hemoptysis, oliguria, metabolic acidosis (or bicarbonate < 20 mmol/l) และ thrombocytopenia (or Plt < 100,000/mm^3)

คำสำคัญ : เลปโตสไปโรสิสที่มีอาการรุนแรง, การเสียชีวิต, ไตวายเฉียบพลัน, ภาวะหายใจล้มเหลว

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