Leptospirosis Outbreak after a Heavy Rainfall Typhoon in the Philippines: Clinical Features, Outcome and Prognostic Factors for Mortality

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ABSTRACT

Background and Objectives. In September 2009, Metro Manila was hit by a heavy rainfall typhoon Ketsana inundating several cities of Metro Manila causing an outbreak of leptospirosis. We analyzed the prognostic factors associated with mortality among leptospirosis patients admitted after the typhoon at nine tertiary hospitals from September to November 2009.

Methods. We reviewed the charts of patients with probable and confirmed leptospirosis. Confirmed leptospirosis was based on any of the following: positive leptospiral culture of blood or urine, single high leptospira microagglutination titer (MAT) of 1:1600 or a fourfold rise in MAT antibody titers or seroconversion. Patients with negative serology or cultures but with history of wading in floodwaters plus any of the following signs and symptoms: fever, headache, myalgia, conjunctival suffusion, diarrhea and abdominal pain, jaundice, oliguria and changes in sensorium were considered probable cases.

Results. We analyzed 332 probable and 259 confirmed leptospirosis patients. Mean age was 37.95 ± 14.09, mostly males (80.2%). Almost all patients (98%) waded in floodwaters. Majority had moderate to severe form of leptospirosis (83%). Acute renal failure was the most common complication (87.1%). Mortality was 11.3% mostly due to pulmonary hemorrhage. On multivariate analysis of confirmed and probable cases, the factors independently associated with mortality were pulmonary hemorrhage (OR 2.75, 95% CI 1.46 to 5.20), severity of the disease (OR 3.85, 95% CI 1.60 to 9.26), thrombocytopenia (OR 3.16, 95% CI 1.22-8.16), duration of illness before admission (OR 0.88, 95% CI 0.78-0.99) and age (OR 1.03, 95% CI 1.00-1.06).

Conclusion. Pulmonary hemorrhage remains a poor prognostic factor and strong predictor of mortality among patients with severe leptospirosis. Early consult through heightened awareness of the public and prompt recognition of leptospirosis among clinicians can decrease the risk for progression to complications of leptospirosis and mortality.

Key Words: leptospirosis, clinical profile, predictors of mortality, typhoon, Philippines, outbreak

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Introduction

Leptospirosis has been recognized as an important global public health problem because of its ability to cause disease in epidemic proportions. Increasing incidence in both developing and developed countries has been reported.[1] Wild and domestic animals act as reservoirs that contaminate the human environment making it an endemic zoonosis. Traditionally considered an occupational risk among persons exposed to contaminated water or infected animal urine, leptospirosis has re-emerged as a major public health concern, particularly in the tropics.[2] Flooding is recognized as a factor increasing the risk for exposure to leptospires through contact with contaminated water or mud.[3] Urban outbreaks of leptospirosis usually cluster in areas with poor sanitation and that remained flooded for quite a time post heavy rainfall.[3] Recent outbreaks after flooding from heavy rainfall raised awareness on the risk of leptospirosis in disaster situations.

On September 26, 2009, typhoon Ketsana (local name Ondoy) hit Metro Manila with heavy rainfall of 455 mm in just 24 hours inundating several cities and municipalities, which was significantly heavier than the recorded average rainfall of 965 t0 4,064 mm per year in the Philippines. Four weeks later, Metro Manila and some surrounding provinces remained underwater. On the average, 680 leptospirosis

cases and 40 deaths from the disease are reported in the Philippines every year. However, following the heavy rainfall in 2009, an increase of 2,292 suspected cases of leptospirosis with 178 deaths (7.8%) were recorded two weeks after the typhoon prompting the Department of Health to declare a leptospirosis outbreak.[4]

Leptospirosis is an acute febrile illness usually presenting with mild nonspecific symptoms but can also have severe fatal complications sometimes. Progression of the disease from mild to severe state can sometimes be fast and irreversible. Subclinical cases are usually very mild, flu-like illnesses with patients recovering spontaneously. Those with the severe form develop complications involving various organs and requiring hospitalization. International studies on clinical profile of leptospirosis patients after flooding were reported[5-8] while local studies on the clinical presentation of leptospirosis patients were done previously but not during an outbreak.[9-11]

We conducted this retrospective observational cohort study to determine the prognostic factors associated with mortality and to describe the clinical features and outcomes of leptospirosis patients after the heavy rainfall typhoon Ondoy. Data derived from this study can be used to guide clinicians in the early recognition and management of leptospirosis during the monsoon months to prevent complications, which can lead to severe morbidity and mortality.

Methods

Setting and Study Population

Patients suspected of leptospirosis admitted from September 28, 2009 to November 30, 2009 to the following hospitals proximal to the major cities flooded by the typhoon were included: University of the Philippines-Philippine General Hospital (UP-PGH), National Kidney and Transplant Institute (NKTI), The Medical City (TMC), University of Santo Tomas Hospital (USTH), Manila Doctors Hospital (MDH), Ospital ng Maynila Medical Center (OMMC), Cardinal Santos Medical Center (CSMC), East Avenue Medical Center (EAMC) and Makati Medical Center (MMC).

The demographic profile, signs and symptoms and clinical course of the patients were obtained through patient interview and chart review. History of wading in flood waters, ingestion of floodwater and flood-related injuries were also asked. All data were recorded in a standardized case report form.

Criteria for probable leptospirosis

Patients with history of wading in floodwater plus any of the following signs and symptoms: fever, headache, myalgia, conjunctival suffusion, diarrhea and abdominal pain, jaundice, decreased urine output and changes in sensorium/meningism were assessed to have probable leptospirosis.

Confirmed Cases

Using the WHO criteria of definitive leptospirosis, laboratory confirmation of the diagnosis was based on any of the following: a) positive leptospiral culture of the blood and/or urine; b) single high leptospira microagglutination titer (MAT) of ≥1: 1600 from blood extracted any time during admission; c) seroconversion from initial negative to a positive antibody titer on second sample; d) fourfold rise in antibody titers by MAT from acute to convalescent. To determine the acute titer, blood was extracted upon consult or admission. Then blood was extracted again 7-10 days after the first extraction or just before discharge to determine the convalescent titer. All culture and serologic examination for leptospirosis were done in a single laboratory, the UP-PGH IDS laboratory.

Data Analysis

Descriptive data were summarized using frequencies and percentages for categorical data. For continuous data, means and standard deviation were computed. Bivariate and multivariable logistic regression analyses were performed to determine the prognostic factors associated with mortality using the Statistical Package for the Social Sciences (SPSS Version 17, Chicago Ill) software. Odds ratios with 95% CI were reported.

To determine the factors associated with mortality with an odds ratio of 2, an estimated mortality of 15-25%, precision of 5% and 80% power, 450 confirmed cases of leptospirosis were needed.

Ethical considerations

This study was technically and ethically approved by the Ethics Review Board of the Philippine General Hospital, University of the Philippines Manila (Ref No. MED 2009-11-10-119; 2009 Dec 21).

Results

Out of 670 possible leptospirosis patients who consulted and/or were admitted in the nine tertiary hospitals in Metro Manila between September 28, 2009 and November 30, 2009 after the typhoon Ondoy, 591 suspected leptospirosis cases were included in the study. We excluded 79 patients who either had no laboratory specimens sent or no available clinical data.

Of the 591 suspected leptospirosis cases, 259 were confirmed by serology and/or culture and 332 were probable leptospirosis. Table 1 is a summary of the demographic characteristics and distribution of the patients included in this study. Majority were men with mean age of 37.95 (SD 14.09) years. The patients who died were statistically significantly older with mean age of 41 years old compared to those who survived with mean age of 37 years. Sex distribution and the proportion of patients with comorbidities did not differ significantly between those who survived and those who

died. Almost all of the cases had a history of wading or swimming in floodwaters (98%). A small percentage also swallowed floodwaters, had open wounds which served as point of entry of the leptospires or were exposed to animal carcasses in the floodwaters. Most patients came from Rizal (18%), followed by Quezon City (14%), Manila (12%), Makati (12%) and Marikina (12%). More patients consulted and eventually were admitted during the first week of illness (33%). Of the nine participating tertiary hospitals, UP-Philippine General Hospital had the most number of cases (30%) followed by the National Kidney and Transplant Institute (25.4%) and The Medical City (9%) (Table 1).

Table 1. Demographic profile and distribution of leptospirosis cases

Characteristic	Confirmed and probable cases of leptospirosis N= 591		Total N=591	p value
	Survived n=524 (%)	Died n= 67 (%)		
Age (Yrs)				
Mean ± SD	37.65 ± 14.05	41.25 ± 13.10	37.95 ± 14.09	0.05
Range	14 – 79	19-60	14 – 79	
Sex				
Male	416 (79.4)	58 (86.6)	474 (80.2)	0.16
Female	108 (20.6)	9 (13.4)	117 (19.8)	
Occupation				
Unemployed	102 (19.5)	10 (14.9)	112 (19.0)	
Government employee	39 (7.4)	1 (1.5)	40 (6.8)	
Laborers	29 (5.5)	1 (1.5)	30 (5.1)	
Businessman	21 (4.0)	0	21 (3.6)	
Student	21 (4.0)	1 (1.5)	22 (3.7)	
Driver	13 (2.5)	2 (3.0)	15 (2.5)	
Self employed	13 (2.5)	2 (3.0)	15 (2.5)	
Teacher	13 (2.5)	0	13 (2.2)	
House help	11 (2.1)	0	11 (1.9)	
Vendor	10 (1.9)	0	10 (1.7)	
With comorbidities	47 (9.0)	2 (3.0)	49 (8.3)	0.09
Residence				
Rizal	93 (17.7)	15 (22.4)	108 (18.3)	
Quezon City	73 (13.9)	8 (11.9)	81 (13.7)	
Manila	65 (12.4)	4 (6.0)	70 (11.8)	
Marikina	62 (11.8)	5 (7.5)	66 (11.2)	
Makati	56 (10.7)	12 (17.9)	68 (11.5)	
Pasig	45 (8.6)	3 (4.5)	48 (8.1)	
Pasay	22 (4.2)	1 (1.5)	23 (3.9)	
Taguig	17 (3.2)	2 (3.0)	19 (3.2)	
Paranaque	13 (2.5)	2 (3.0)	15 (2.5)	
Laguna	12 (2.3)	4 (6.0)	16 (2.7)	
Bulacan	9 (1.7)	1 (1.5)	10 (1.7)	
Mandaluyong	9 (1.7)	2 (3.0)	11 (1.9)	
Cavite	8 (1.5)	1 (1.5)	9 (1.5)	
Malabon	4 (0.8)	0	4 (0.7)	
San Juan	4 (0.8)	2 (3.0)	6 (1.0)	
Nueva Ecija	3 (0.6)	2 (3.0)	5 (0.8)	
Valenzuela	3 (0.6)	2 (3.0)	5 (0.8)	
Batangas	3 (0.6)	0	3 (0.5)	
Pateros	2 (0.4)	0	2 (0.3)	
Las Pinas	2 (0.4)	0	2 (0.3)	
Waded / swam in floodwaters	513 (97.9)	65 (97.0)	578 (98.0)	0.65
Swallowed floodwaters	56 (10.7)	2 (3.0)	58 (9.8)	0.05
Presence of wound	91 (17.4)	4 (6.0)	95 (16.1)	0.02
Exposure to animal carcass	35 (6.7)	4 (6.0)	39 (6.6)	1.00
Duration of Illness before admission				
<7 days	186 (35.5)	10 (14.9)	196 (33.2)	
>7 days	54 (10.3)	3 (4.5)	57 (9.6)	
Hospital				
UP-PGH	162 (30.9)	17 (25.4)	179 (30.3)	
NKTI	130 (24.8)	20 (29.9)	150 (25.4)	
The Medical City	52 (9.9)	2 (3.0)	54 (9.1)	
UST Hospital	20 (3.8)	2 (3.0)	22 (3.7)	
Manila Doctors Hosp	13 (2.5)	0	13 (2.2)	
Ospital ng Maynila	13 (2.5)	0	13 (2.2)	
Cardinal Santos MC	5 (1.0)	0	5 (0.9)	
East Av Med Center	80 (15.3)	2 (3.0)	82 (13.9)	
Makati Medical Center	11 (2.1)	1 (1.5)	12 (2.0)	

Majority of the confirmed leptospirosis cases had positive serology (68%). Single high MAT titers were seen in 49%, 13% had a four-fold rise while 6% had seroconversion. Of the 259 confirmed leptospirosis, 55 (21%) had positive leptospiral blood culture and only two patients had positive urine culture. Ten percent were positive on both serology and culture (Table 2).

Table 2. Laboratory confirmed leptospirosis cases

Laboratory Diagnosis	Number n=259 (%)
Positive Culture	57 (22.0)
Blood cultures	55 (21.2)
Urine cultures	2 (0.8)
Serology	176 (68.0)
Single high titer	127 (49.0)
Fourfold rise	33 (13.0)
Seroconversion	16 (6.1)
Positive Serology and Culture	26 (10.0)

Clinical and Laboratory Features

Fever was the most common presenting symptom followed by myalgia and/or calf tenderness, malaise and headache. Conjunctival suffusion was seen in more than half of the patients (53.1%). Twenty percent of the patients came in hypotensive and the proportion of patients with hypotension was significantly greater in the mortality group compared to the group that survived. Gastrointestinal symptoms reported were abdominal pain (56.8%), nausea and vomiting (49 %), diarrhea (38.6%), and jaundice (29.9%). Pulmonary signs and symptoms included cough (27.6%), dyspnea (17.8%), crackles (19.3%), and hemoptysis (11.8%). Oliguria was present in 51%. Bleeding tendencies such as hematuria was seen in 19.8%, gastrointestinal bleeding in 12.5% and other hemorrhagic signs like epistaxis or petechiae in 12.7%. The proportion of patients presenting with hypotension, jaundice, oliguria, dyspnea and rales on auscultation were significantly greater among those who died compared to the patients who survived (Table 3).

More than half of the study population (58.4%) had elevated creatinine. Thrombocytopenia or platelet count of <100,000/mm3 was present in only 17%. Leukocytosis was more commonly seen in 40.3% of patients. Only 23% had an elevated serum AST level and a smaller percentage (14.2%) had hyperkalemia. There were significantly more patients with azotemia, defined as elevated creatinine level of >176umol/L, and thrombocytopenia among those who died compared to those who survived (Table 3).

Table 3. Clinical and laboratory features of leptospirosis cases

Clinical features	Confirmed and probable cases of leptospirosis N= 591		Total N=591	p value
	Survived n=524 (%)	Died n= 67 (%)		
Non-specific				
Fever	495 (94.5)	55 (82.1)	550 (93.1)	0.0009
Myalgia/calf tenderness	369 (70.4)	38 (56.7)	407 (68.9)	0.02
Malaise	362 (69.1)	43 (64.2)	405 (68.5)	0.42
Headache	273 (52.1)	22 (32.8)	295 (49.9)	0.003
Chills	211 (40.3)	17 (25.4)	228 (38.6)	0.02
Conjunctival suffusion	284 (54.2)	30 (44.8)	314 (53.1)	0.15
Hypotension	93 (17.7)	24 (35.8)	117 (19.8)	0.0005
Gastrointestinal				
Abdominal pain	300 (57.3)	36 (53.7)	336 (56.8)	0.58
Nausea/Vomiting	259 (49.4)	32 (47.8)	291 (49.2)	0.80
Diarrhea	206 (34.9)	22 (32.8)	228 (38.6)	0.30
Jaundice	146 (27.8)	31 (46.3)	177 (29.9)	0.002
GI bleeding	66 (12.6)	8 (11.9)	74 (12.5)	0.88
Renal				
Oliguria	260 (49.6)	42 (62.7)	302 (51.1)	0.04
Hematuria	104 (19.8)	13 (19.4)	117 (19.8)	0.93
Pulmonary				
Cough	149 (28.4)	14 (20.9)	163 (27.6)	0.19
Dyspnea	87 (16.6)	18 (26.9)	105 (17.8)	0.04
Crackles/rales	86 (16.4)	28 (41.8)	114 (19.3)	<0.0001
Hemoptysis	61 (11.6)	9 (13.4)	70 (11.8)	0.67
Hematologic				
Hemorrhagic signs (epistaxis, petechiae)	62 (11.8)	13 (19.4)	75 (12.7)	0.08
Laboratory				
Elevated CREA (>176umol/L)	291 (55.5)	54 (80.6)	345 (58.4)	0.0001
Leukocytosis (wbc>12,000)	204 (38.9)	34 (50.7)	238 (40.3)	0.06
Elevated BUN (>10-20mg/dL)	129 (24.6)	10 (14.9)	139 (23.5)	0.08
Elevated AST (> 37 SI Units)	121 (23.1)	13 (19.4)	134 (22.7)	0.50
Thrombocytopenia (<100,000/mm3)	75 (14.3)	27 (40.3)	102 (17.3)	<0.0001
Elevated serum K (>4)	71 (13.6)	13 (19.4)	84 (14.2)	0.20

Outcomes of Confirmed Leptospirosis

Majority of the patients had moderate to severe form of leptospirosis (83%). Moderate to severe leptospirosis refer to patients with any of the following: beginning renal failure (azotemia, decreased urine output), dyspnea with or without need for oxygen support, basal infiltrates on chest X-ray, conjunctival suffusion, abdominal pain, and meningismus.[12] Acute renal failure (87.1%) was the most common complication of leptospirosis in this study. Pulmonary hemorrhage was reported in 5.2% of the population, while myocarditis and meningitis in 2.7% and 2.4%, respectively. Nevertheless, majority of the patients were discharged improved (95%). The proportion of patients with acute renal failure on admission and pulmonary hemorrhage were significantly greater among those who died compared to those who survived (Table 4).

The mortality rate of leptospirosis patients in this study was 11%. Most of those who died had renal failure upon admission (82.1%). Weil's syndrome, the most distinctive form of severe leptospirosis characterized by impaired hepatic and renal function with signs of hemorrhage,[12] was seen in 33% of the mortalities. In addition, almost 25% of those who died presented with pulmonary hemorrhage (Table 4).

Table 4. Complications of leptospirosis

	Confirmed and probable cases of leptospirosis N= 591		Total N=591	p value
	Survived n=524 (%)	Died n= 67 (%)		
Renal Failure	459 (87.6)	56 (83.6)	515 (87.1)	
upon admission	348 (66.4)	55 (82.1)	403 (68.2)	0.0001
progression	39 (7.4)	8 (11.9)	47 (8.0)	0.16
Pulmonary hemorrhage	14 (2.7)	17 (25.4)	31 (5.2)	<0.0001
Meningitis	11 (2.1)	3 (4.5)	14 (2.4)	0.23
Myocarditis	11 (2.1)	1 (1.5)	12 (2.0)	0.34
Weil's Disease	166 (31.7)	22 (32.8)	188 (31.8)	0.85

Table 5. Predictors of mortality among confirmed and probable cases: multivariate analysis

Risk Factor	OR (95% CI) for confirmed and probable cases	p-value	OR (95% CI) for confirmed cases	p-value
Age	1.03 (1.00, 1.06)	0.04	2.42 (0.58, 10.10)	0.22
Sex	1.33 (0.49, 3.63)	0.58	--	--
Exposure to flood	0.29 (0.02, 4.04)	0.36	--	--
Days of illness before admission (>7days)	0.88 (0.78, 0.99)	0.03	--	--
Presence of comorbidities	0.42 (0.11, 1.57)	0.20	0.94 (0.14, 6.19)	0.95
Thrombocytopenia	3.16 (1.22, 8.16)	0.02	1.70 (0.36, 8.08)	0.50
Renal dysfunction	0.73 (0.20, 2.61)	0.62	--	--
Pulmonary hemorrhage	2.75 (1.46, 5.20)	0.002	77.0 (12.84, 462)	<0.001
Severity of the disease	3.85 (1.60, 9.26)	0.003	--	--
Myocarditis	--	--	2.46 (0.13, 45.48)	0.54
Weil's syndrome	--	--	0.72 (0.12, 4.33)	0.72

Table 6. Predictors of pulmonary hemorrhage

Risk Factor	OR	95% CI	p-value
Age	1.7	0.64-4.47	0.29
Sex	0.67	0.13-3.41	0.63
Oliguria	1.82	0.51-6.51	0.36
Hemoptysis	2.35	0.76-7.27	0.14
Hypotension	6.05	2.10-17.37	0.001
Jaundice	2.33	0.79-6.88	0.13
Thrombocytopenia	1.11	0.35-3.48	0.86
Elevated creatinine	2.66	0.52-13.55	0.24

On multivariate analysis, the independent predictors of mortality for confirmed and probable cases were age (OR 1.03, 95% CI 1.00-1.06), pulmonary hemorrhage (OR 2.75, 95% CI 1.46 to 5.20), severity of the disease (OR 3.85, 95% CI 1.60 to 9.26) and thrombocytopenia (OR 3.16, 95% CI 1.22-8.16). On the other hand, consultation 7 days or more from the duration of illness before admission was associated with improved survival (OR 0.88, 95% CI 0.78-0.99). On sensitivity analysis of confirmed cases, only pulmonary hemorrhage remained independently associated with mortality (OR 77, 95% CI 12.8 to 462) (Table 5). On further analysis on the predictors of pulmonary hemorrhage, hypotension was identified as independently associated with development of pulmonary hemorrhage (OR 6.05, 95% CI 2.10 to 17.37) (Table 6).

Discussion

This large cohort of moderate to severe leptospirosis provides comprehensive data on the clinical course, outcome and predictors of mortality among cases observed during an outbreak from an unusually heavy rainfall from Typhoon Ketsana that hit Metro Manila. Previous studies done in the country were mostly single center studies describing the clinical features and outcomes of seasonal leptospirosis. Our cohort included a purposive sample of patients from almost all areas of Metro Manila admitted in nine hospitals proximal to the areas affected by the typhoon. In the Philippines, few studies reported factors associated with mortality of

leptospirosis (Table 7). This leptospirosis outbreak cohort of 2009 recorded a mortality rate of 11% which is within the reported range of mortality rates of leptospirosis from 5% to 40%.[13] Since this study was conducted in a hospital setting, we expected a high representation of patients with severe disease. Interestingly, the non-specific prodromal symptoms of fever, headache, malaise, myalgia and calf tenderness were more commonly reported among the patients who survived compared to those who died. As expected, the signs of severity were more commonly observed among those who died, i.e., hypotension on admission, oliguria, jaundice, dyspnea and crackles on auscultation, elevated creatinine and thrombocytopenia.

The earlier cohorts on seasonal leptospirosis at the Philippine General Hospital identified oliguria as a significant predictor of mortality with oliguric patients having twice the risk of dying than non-oliguric patients.[14] Elevated creatinine, low platelet count, low HCO3, low alkaline phosphatase and type of treatment received (dopa-furo-mannitol vs dopa-furo among oliguric patients) were the identified predictors of oliguria and eventually mortality.[15] A smaller cohort of presumptive leptospirosis patients in another government hospital described that all patients who died had oliguric

renal failure. Mortality rate was 18% and factors associated with mortality on univariate analysis were leukocytosis, thrombocytopenia, evidence of bleeding, oliguria, length of time from onset of disease up to the time the patient sought consult and evidence of liver dysfunction.[16]

In contrast to the earlier single-center studies on seasonal leptospirosis that reported factors associated with mortality, our study identified pulmonary hemorrhage as a strong independent predictor of mortality (Table 7). Although earlier studies did report pulmonary hemorrhage[17] and acute renal failure[18] among the most common causes of death in leptospirosis, no further analysis was done. One descriptive study observed that mortality was higher in the thrombocytopenic group with hemorrhagic causes.[17]

The incidence of pulmonary involvement in leptospirosis varies from 20% to 70%.[19] Pulmonary manifestations were previously reported to be less prominent with hemoptysis being observed in 3-25% of patients and chest pain in 10%.[19] Epidemic cohorts of leptospirosis in other countries have reported pulmonary manifestations dominating the clinical picture. These cohorts have also identified pulmonary hemorrhage as a significant predictor of mortality (Table 8).

Table 7. Comparison of local studies that reported factors associated with mortality of leptospirosis

	Edmilao[14] 1995	Villela[15] 2000	Orpilla-Bautista[16] 2002	This study
No. of leptospirosis cases	191	300	83	591
No. of deaths	16/191 (8.5%)	52/300 (17%)	15/83 (18%)	67/591 (11.3%)
Prognostic factors of mortality	Oliguria	Oliguria Type of treatment received Low HCO3 Low AlkPhos High creatinine Low platelet count	Leukocytosis Thrombocytopenia Evidence of bleeding Oliguria Delayed consultation (> 6 days)	Age Thrombocytopenia Pulmonary hemorrhage Severity of the disease

Table 8. Predictors of mortality in leptospirosis compared with cohorts from other countries

	France[20] 1997	Brazil[21] 1999	India[22] 2004	Brazil[23] 2008	Indonesia[24] 2009	India[25] 2014	This Study Philippines
No. of lepto-spirosis cases	68	110	282	840	55	101	591
No. of deaths	12 (18%)	24 (22%)	17 (6.03%)	119 (17%)	8 (14.5%)	17 (16.8%)	67/591 (11.3%)
Prognostic factors of mortality	Dyspnea (OR 11.7; CI 2.8-48.5)	Oliguria (OR 9.0; CI 1.81-44.6)	Lung involvement (OR 5.3; CI 1.25–22.67)	Age > 40 years (OR 2.2; CI 1.1–4.3)	Pulmonary involvement (OR 9.9;CI 1.17-84.03)	High aspartate/alanine aminotransferase ratio (AAR) (HR 1.208, 95% CI 1.05–1.39)	Age
	Oliguria (OR 9; CI 2.1-37.9)		Meningism (OR 6.08; CI1.40-26.41)	Pulmonary involvement (OR 6.0; CI 3.0–12.0)		Delayed antibiotic therapy (HR 1.30, 95% CI 1.08–1.57)	Days of illness before admission (>7d)
	Leukocytosis (OR 2.5; CI 1.8-3.5)			Oliguria (OR 3.0; CI 1.2–9.0)			Thrombocyto-penia
	Abnormality on ECG finding (OR 5.9; CI 1.4-24.8)			Platelets < 70,000 (OR 2.2; CI 1.2–4.7)			Pulmonary hemorrhage
	Alveolar infiltrates on chest X-ray (OR 7.3; CI 1.7-31.7)			Creatinine > 3.0 mg/dL (OR 2.3; CI 1.1–5.)			Severity of the disease

As early as 1997, in a study of 68 leptospirosis patients at the emergency department of West Indies, France, pulmonary manifestations such as dyspnea and alveolar infiltrates on chest radiographs were included in the five factors identified to be independently associated with mortality.[20] In a retrospective cohort of patients with Weil's disease in Brazil, dyspnea, and pulmonary rales were also significant predictors of mortality on univariate analysis however on logistic regression, only oliguria was the identified independent factor associated with death.[21] Moreover, another study reported lung involvement (dyspnea and hemoptysis) and central nervous system manifestation (meningism) as significant predictors of death among leptospirosis patients.[22] In 2008, a case control study ascertaining prognostic factors associated with fatal outcomes in severe leptospirosis, concluded that pulmonary involvement was the strongest risk factor for death.[23] Pulmonary involvement was also cited as strong predictor of mortality among 55 severe leptospirosis patients admitted at Dr. Sardjito Hospital, Yogyakarta, Indonesia from 2003 to 2007.[24] A recent study in India, however, identified high aspartate/alanine transferase ratio and delayed antibiotic administration as significant predictors of mortality.[25]

Pulmonary hemorrhage is a consistent predictor of mortality as shown in previous studies.[20,22-24] Acute respiratory distress syndrome is the usual complication of pulmonary hemorrhage and is the immediate cause of death of the patients.[26] Leptospirosis patients who developed respiratory symptoms have high mortality rates ranging from 4.8% to 11%.[27] Hypotension was identified as a predictor of pulmonary hemorrhage in our cohort. Hypotension indicates impairment of the microcirculation and increased capillary permeability from vasculitis or even unrecognized bleeding. Vasculitis is the same pathogenesis for pulmonary hemorrhage in leptospirosis. Hence, presence of hypotension may indicate severe vasculitis and can predict impending pulmonary hemorrhage.

This large cohort of confirmed and probable cases of moderate to severe leptospirosis complements the results of previous cohorts of seasonal leptospirosis done in the country. The clinical findings in this outbreak compare very well with other local retrospective studies involving patients with seasonal leptospirosis. Acute renal failure and pulmonary hemorrhage were the two most common complications of the disease that influences survival. Prompt recognition and advances in the modalities for management of acute renal failure may have contributed to improved survival rates despite relatively delayed consultations of one week or more from onset of illness in this cohort. Our study identified pulmonary hemorrhage as a prognostic factor strongly associated with mortality in an outbreak setting.

Conclusion

The clinical manifestations and outcomes of leptospirosis in an outbreak setting did not vary significantly with seasonal-related leptospirosis. Pulmonary hemorrhage remains a poor prognostic factor and strong predictor for mortality among patients with severe leptospirosis. This emphasizes that, whether in seasonal cases or during outbreaks of leptospirosis, the need for awareness of the disease by the public and high index of suspicion for leptospirosis among clinicians are necessary to decrease morbidity and mortality.

Leptospirosis should always be included in the differential diagnosis of patients presenting with fever together with nonspecific prodromal symptoms following exposure to flood. Patients presenting with pulmonary manifestations, hypotension and oliguria should be monitored more closely and more aggressively.

We recommend molecular studies to determine whether the distribution of leptospirosis serovars and strains in the country has changed through the years in the current setting of climate change and whether these could have contributed to changes in the patterns of presentation and severity of the disease. Studies on the effectiveness of interventions to address pulmonary hemorrhage are also recommended.

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