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Bonus RB, Maramba-Lazarte CC. Predictors of Mortality in Leptospirosis

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The authors declare that the data presented are original material and have not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all the authors, who have met the requirements for authorship.

ORIGINAL ARTICLE

PREDICTORS OF MORTALITY AMONG PEDIATRIC PATIENTS WITH LEPTOSPIROSIS: A MULTICENTER RETROSPECTIVE STUDY

ABSTRACT

Objective: Leptospirosis in children is one of the most common diagnostic dilemmas, hence this study was performed to determine the clinical profile, outcome and risk factors associated with mortality in patients seen at tertiary government hospitals from January 2008 to December 2012.

Methods: A case-control retrospective study was done among admitted patients at UP-PGH, SLH, and RITM. Descriptive statistics and multiple logistic regressions were utilized.

Results: Among the 404 leptospirosis cases included in the study, 94% were male, with 43% belonging to 16-18-year-old age group (age range 3 to 18 years old). A higher occurrence was noted during the rainy season and in Manila.

Clinical findings include fever, abdominal pain, calf tenderness, vomiting and conjunctival suffusion. Significant correlation was noted in patients with jaundice (p-value 0.014; OR 6.293, CI 1.449-27.335), dyspnea (p-value 0.004; OR 7.880, CI 1.967-31.561) and cardiac abnormality (p-value 0.042; OR 15.343, CI 1.106-212.853).

Abnormal laboratory findings include neutrophilia, azotemia, creatinemia, anemia, elevated bilirubin levels and thrombocytopenia. Prolonged prothrombin time was associated with poor outcome (p-value 0.004, OR 23, CI 2.79-189.67).

Penicillin was the drug of choice given to 96.8%. 94.6% of cases who had oliguric renal failure were conservatively converted to non-oliguric type. 5.4% underwent peritoneal dialysis and survived. Inotropes were used in 93% of non-survivors.

The case fatality rate was 3.5% with the cause of death mostly due to Weil's disease. The average hospital stay among survivors was 6.8$\pm$3.3 days as compared with 1.8$\pm$1.9 days in nonsurvivors. Shorter hospital stay (p-value 0.00; OR 3.514, CI 2.115-5.839), as well as inotropic support (p-value 0.035; OR 62.511, CI 1.33-2949.134), were associated with poorer outcome, but these findings can be attributed to late presentation of cases at the hospital for admission.

Conclusion: A5 year review of patients with leptospirosis showed that jaundice, dyspnea, cardiac abnormality and prolonged prothrombin time were predictive of mortality.

KEYWORDS:
Leptospirosis, predictors of mortality, Weil's syndrome

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INTRODUCTION

Leptospirosis is a re-emerging zoonotic infection that is often under-recognized in children. The recent data as of August 2012 from the Department of Health reported a total of 2,471 leptospirosis cases, which is 62.35% higher as compared to 1,522 cases in 2011. The case fatality rate in children was 1% in those aged 1 to 10 years old approximately and 2.8% in those aged 11 to 20 years old[2].

Only a handful of studies were conducted describing the clinical profile of leptospirosis among Filipino children; most of them were conducted among adults. The case-fatality rate is lower in children and adolescents than in adults but there is a lack of studies conducted specifically to compare the prognosis of leptospirosis in children[3,4].

The disease, especially in the pediatric populations, are among the most common diagnostic dilemmas, hence the diagnosis is often missed. Early diagnosis is mainly clinical (based on the characteristic signs and symptoms), and epidemiological (based on the history of wading and contact with animals) since laboratory diagnosis (serology or culture) can only be obtained on the latter course of the disease. This study aimed to determine the clinical profile, outcome and risk factors of leptospirosis in pediatric patients seen at three tertiary government hospitals from January 2008 to December 2012.

METHODOLOGY

This was a case-control retrospective study of all pediatric patients aged 0 to 18 years old diagnosed with leptospirosis based on the WHO criteria[20] admitted at the University of the Philippines-Philippine General Hospital (UP-PGH), Research Institute for Tropical Medicine (RITM) and San Lazaro Hospital (SLH) from January 2008 to December 2012. Data on demographic characteristics, clinical and laboratory profile and outcomes were obtained using a standard data collection form adapted from the Philippine Clinical Practice Guidelines on the Diagnosis, Management, and Prevention of Leptospirosis in 2010[5]. The diagnosis was based on the clinical (fever, headache, bilateral conjunctival suffusion, meningism, muscle pain, jaundice, and albuminuria or nitrogen retention), epidemiological (contact with animals at home, work, leisure or in travel, or contact with known or possibly contaminated water) and bacteriological laboratory findings presumptive of leptospirosis according to the WHO criteria in 2011. Both probable and laboratory-confirmed cases of leptospirosis were included in the study. These patients were classified into two groups depending on their outcome: the cases were the nonsurvivors, while the control group was those who recovered (survivor group) from the disease. The clinical features and laboratory parameters were compared in both groups and possible risk factors predictive of poor outcome or mortality were identified.

Pediatric patients 18 years old and below, diagnosed as probable or laboratory-confirmed leptospirosis cases seen and admitted to the emergency room and pediatric wards from the three tertiary government hospitals from January 2008 to December 2012 were included in the study.

The sample size was calculated based on the data from the Philippine Integrated Disease Surveillance and Response (PIDSR), assuming that the number of cases in the three hospitals is similar. The total number of leptospirosis cases aged 0 to 18 years old from January 1, 2008, to December 31, 2008, was 4,368 patients with total deaths of 131[6]. Having the standard 95% confidence level and power of 80%, the unadjusted sample size is equal to 284 cases (per group), a total of 568 cases (nonsurvivors and survivors). Given that the proportion of non-survivors was considerably smaller than the survivors (more or less 5% of total

cases) the sample size was re-adjusted. The adjusted sample size is now equal to 90 cases per group or a total of 180 cases.

Leptospirosis patients diagnosed clinically or laboratory-confirmed cases were included in the study. The list of patients was obtained from the inpatient and outpatient database with International Classification of Diseases, 10th revision, coding from the medical records sections (UP-PGH and RITM) and Epidemiology unit (SLH). Data were extracted from the medical charts, after obtaining approval of the institutional/ethical review board committee of each hospital. Limitation of the study was based on the completeness and reliability of their hospital records. Demographic characteristics, clinical and laboratory profiles, and outcome were collected using the standard data collection form. The factors predictive of poor outcome include clinical and laboratory features such as: fever, conjunctival suffusion, signs of dehydration, respiratory involvement (cough, dyspnea, hemoptysis, abnormal chest PE and x-ray findings), cardiovascular abnormality, gastrointestinal system involvement (diarrhea, abdominal pain, vomiting, jaundice, abnormal liver function test), hematological abnormality (anemia Hgb <130mg/dL, leukocytosis WBC >10,000/mm^3 and thrombocytosis platelet count <150,000/mm^3), central nervous system abnormalities (headache and meningism), renal system involvement (hematuria, decreased urine output, albuminuria, blood urea >60 mg/dl, serum creatinine >2 mg/dl), electrolyte abnormalities (hypokalemia, hyperkalemia, hyponatremia) and muscle or joint pains. Data were collated and analyzed.

Microsoft Excel was utilized for data collection and processing, and statistical analysis was done using SPSS version 21 and 'R' software. Pearson correlation was done to check for plausible correlations between variables. Various statistical methods were employed for hypothesis testing and test of associations between parameters, as appropriate, which included both parametric and non-parametric methods, as well as multivariate analysis. Confidence level was set at 95% with a p-value of $P < 0.05$ deemed as statistically significant.

RESULTS

A total of 480 cases of clinically diagnosed leptospirosis were included in this study but only 410 charts were retrieved from the medical records sections. Information on death or survival was missing for six patients transferred to other hospitals. Hence, of the 480, 404 charts were complete and included in the study, the biggest sample population of leptospirosis in children to date. The comparison was made between survivors with 390 patients (96.5%) and nonsurvivors with 14 cases (3.5%).

In this multi-center, 5-year study, 380 cases (94%) were male and 24 cases (6%) were female. Age ranges from 3 to 18 years old with a mean of 14.3 $\pm$ 3.2 years. The majority of cases were between 16 to 18 years old.

The most number of cases were noted in August 2012 with 126 cases (31.2%) which were observed after the Southwest monsoon "Habagat" and 74 cases (18.3%) on October 2009 which was

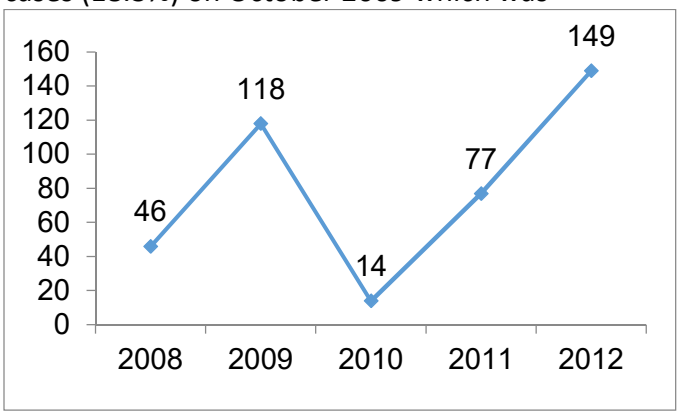

Figure 1. Number of Leptospirosis patients by year of Infection

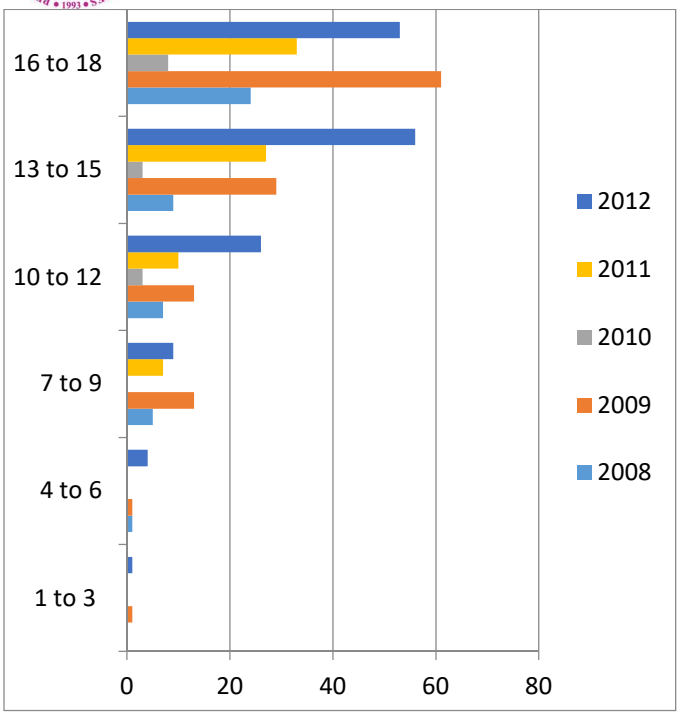

Figure 2. Number of Cases by Age and Year of Infection.

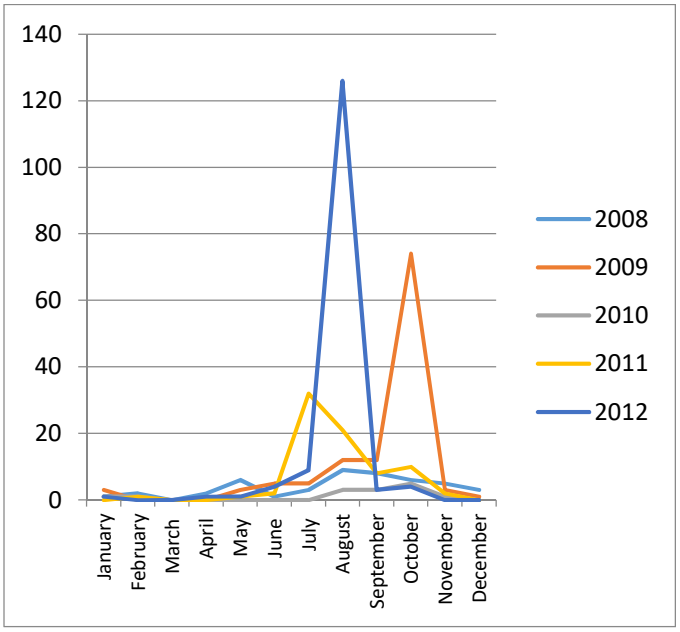

Figure 3. Number of Cases by Month and Year of infection

Table 1. Number of Cases by Location and where Admitted

Region	Cities/ Provinces	Hospital			Total
		SLH	PGH	RITM	
NCR	Manila	78	14		92
	Malabon	52	3		55
	Caloocan	48			48
	Quezon City	43	1		44
	Paranaque	21	2		23
	Pasay	15	4		19
	Valenzuela	18			18
	Navotas	17	1		18
	Taguig	4	7		11
	Muntinlupa	1	5	3	9
	Las Pinas	3	4		7
	Mandaluyong	3	2		5
	Marikina	5			5
	Makati	2	2		4
	Pasig	1	1		2
	San Juan	1			1
4-A	Rizal	11	1		12
	Cavite	6	3	1	10
	Laguna	3		1	4
	Quezon	2			2
3	Bulacan	14			14
	Nueva Ecija	1			1
	TOTAL	**349**	**50**	**5**	**404**

Table 2. Number of Cases by Exposure

Exposure	Survivors	Non-survivors	Total	Percent
With exposure	343	12	355	88
Flood	7	0	7	1.7
water	3	0	3	0.7
River	2	0	2	0.5
Rice field	1	0	1	0.2
Occupational exposure				
Well				
No exposure	21	2	23	5.7
No available data	13	0	13	3.2
Total	**390**	**14**	**404**	**100**

observed after the typhoon "Ondoy". Cases were observed all year-round but more common in the months of August and October, 171 (42.3%) and 99 (24.5%) cases, respectively which corresponded to the rainy season.

In the 17 cities and 5 provinces included in the study, the reported cases of leptospirosis were highest in Manila that ranked first with 92 cases (22.8%), followed by Malabon with 55 cases (13.6%) and Caloocan with 48 cases (11.8%). Considering the location of the hospitals, SLH and UP-PGH catered most cases from the NCR region. Patients from the northern part of Luzon usually go to SLH while most cases in the southern part of Manila goes to UP-PGH and RITM.

The majority of cases had a history of possible exposure to water contaminated with leptospires through wading or swimming in flood water with 355 cases (87.9%). Twenty-three cases (5.7%) deny any exposure while 13 cases (3.2%) had no available data in the chart. Three cases (0.7%) that were exposed to rice field water developed Weil's syndrome and 2 cases (0.5%) were exposed to animals by working at a pet shop and marketplace, respectively.

Admitting Diagnosis

Leptospirosis was the admitting impression in 182 cases (45%). It was considered in most cases due to the history of wading to flood water with acute onset of fever and other renal manifestations. Weil's disease was seen in 138 cases (34.2%) manifested with jaundice, renal and bleeding abnormalities. Dengue fever, viral hepatitis, and typhoid fever were mostly the differential diagnoses noted.

Initial Symptoms

Fever was the primary presenting symptom of all non-survivors (100%) and the most common initial presenting symptom of survivors seen in 395 cases (98%). Symptoms such as calf pain and decreased urine output which are clinically more indicative of leptospirosis were only present in 1% of cases among nonsurvivors (other nonspecific symptoms are summarized in Table 7). In both survivors and non-survivors, almost all cases (96%) had the onset of fever less than seven days prior to admission, with 47% presenting in less than four days before consult. The onset of illness varies from one to 14 days - with an average of 4.9 $\pm$ 2.3 days.

Chief Complaint

For both groups, decreased urine output (19.3%) was the most common cause of consult, followed by fever (17.8%), abdominal pain (15%), jaundice (13.4%) and calf tenderness (9%). A few cases of jaundice (5 subjects), dyspnea (3 subjects), and edema (1 subject) were also seen among non-survivors.

Clinical Manifestations

In both survivors and non-survivors, the most common clinical findings include fever (100%) abdominal pain (76.5%), calf tenderness (76%) and vomiting (74.2%). Conjunctival suffusion (69%), headache (50%), and malaise (45%) were likewise present among a significant number of subjects for both groups. Other manifestations include oliguria/anuria (41%), jaundice (34%), bleeding diathesis, as well as various respiratory and cardiac symptoms. Wound lesions were also seen in 62 cases (15.3%), located mostly in the lower extremities.

Table 3. Admitting Impressions for the Leptospirosis Cases

Initial Impression	Survivors	Non-survivors	Total	Percent
Leptospirosis	180	2	182	45
Leptospirosis in Weil's	131	7	138	34.2
Dengue fever	50	2	52	13
Hepatitis	11	1	12	3
Typhoid fever	5	1	6	1.5
Gastroenteritis	4	1	5	1.2
Urinary tract infection	5	0	5	1.2
Meningitis/encephalitis	2	0	2	0.5
Acute appendicitis	1	0	1	0.2
Systemic viral illness	1	0	1	0.2
Total	**390**	**14**	**404**	**100**

Table 4. Number of Cases by First Presenting Symptom

Symptoms	Survivors	Non-survivors	Total	Percent
Fever	381	14	395	98
Calf pain	2	0	2	0.5
Decreased urine output	2	0	2	0.5
Vomiting	1	0	1	0.2
Abdominal pain	1	0	1	0.2
Conjunctival suffusion	1	0	1	0.2
Diarrhea	1	0	1	0.2
Dizziness	1	0	1	0.2
Total	**390**	**14**	**404**	**100**

Table5. Number of Cases by Onset of Fever prior to Admission

Number of days	Survivors	Non-survivors	Total	Percent
≤ 4	187	3	190	47
5 to 7	181	10	191	47.3
8 to 10	10	0	10	2.5
> 10	12	1	13	3.2
Total	**390**	**14**	**404**	**100**
Mean onset of illness in days	4.8 ± 2.3	5.9 ± 2.6	4.9 ± 2.3	

Table 6. Number Of Cases By Chief Complaint

Symptoms	Survivors	Non-survivors	Total	Percent
Decreased urine output	73	5	78	19.3
Fever	72	0	72	17.8
Abdominal pain	60	0	60	15
Jaundice	49	5	54	13.4
Calf tenderness	36	0	36	9
Vomiting	19	0	19	4.7
Dyspnea	15	3	18	4.4
Conjunctival suffusion	17	0	17	4.2
Diarrhea	16	0	16	4
Hematuria	5	0	5	1.2
Meningism/altered sensorium	4	0	4	1
Icteric sclera	4	0	4	1
Melena	4	0	4	1
Malaise/body weakness	4	0	4	1
Epistaxis	3	0	3	0.7
Hematemesis	2	0	2	0.5
Edema	1	1	2	0.5
Hemoptysis	1	0	1	0.2
Headache	1	0	1	0.2
Gum bleeding	1	0	1	0.2
Dysuria	1	0	1	0.2
Chest pain	1	0	1	0.2
Dizziness	1	0	1	0.2
Total	**390**	**14**	**404**	**99.9**

Table 7. Number of Cases by Sex and Year of Infection

	Survivors n (%)	Non-survivors n (%)	Total N (%)	Odds ratio (95% CI)	Mean (years) [std dev]	p-value	Cases per Year				
							2008	2009	2010	2011	2012
Male	366 (93.8)	14 (100)	380 (94)	59936156.13 (0)	14.4 ±3.2	0.998	44	108	13	73	142
Female	24 (6)	0	24 (6)	-	12.7 ±3.1	-	2	10	1	4	7
Total	**390**	**14**	**404**		**14.3 ±3.2**		**46**	**118**	**14**	**77**	**149**

Table 8. Clinical Findings of Leptospirosis patients

	Survivors (390) n (%)	Non-survivors (14) n (%)	Total 404 N (%)	Odds ratio (95% CI)	p-value
Age (mean age in years)	14.2 ± 3.3	15.6 ±1.9	14.3 ± 3.2	0.17 (0)	1.00
Male Sex	366 (93.8)	14 (100)	380 (94)	59936156.13 (0)	0.998
Onset of illness to admission (mean days)	4.8 ± 2.3	5.9 ± 2.6	4.9 ± 2.3	1.177 (0.968-1.432)	0.102
Average hospital stay in days	6.8 ± 3.3	1.8 ± 1.9	6.5 ± 3.4	3.5 (2.115-5.839)	0.000
Weil's disease	128 (32.8)	10 (71.4)	138 (34.1)	5 (1.575-16.631)	0.007
Systemic					
Fever	390 (100)	14 (100)	404 (100)		1.00
Malaise	171 (43.8)	11 (78.6)	182 (45)	2.949 (0.656-13.263)	0.158
Chills	39 (10.)	3 (21.4)	42 (10.4)	4.797 (0.862-26683)	0.073
Signs of dehydration	35 (9)	3 (21.4)	38 (9.4)	1.939 (0.326-11.526)	0.467
Edema	14 (3.6)	1 (7.1)	15 (3.7)	1.655 (0.123-22.315)	0.704
Gastrointestinal					
Abdominal pain	298 (76.4)	11 (78.6)	309 (76.5)	1.026 (0.179-5.881)	0.977
Vomiting	291 (74.6)	9 (64.3)	303 (74.2)	0.564 (0.127-2.516)	0.453
Diarrhea	98 (25.1)	5 (35.7)	103 (25.5)	0.8 (0.181-3.532)	0.768
Anorexia	53 (13.6)	3 (21.4)	56 (13.9)	0.506 (0.107-2.384)	0.389
Hepato-biliary					
Jaundice	128 (32.8)	10 (71.4)	138 (34.1)	6.293 (1.449-27.335)	0.014
Hepatomegaly	19 (4.9)	3 (21.4)	22 (5.4)	0.096 (0.018-0.508)	0.006
Genito-urinary					
Oliguria	152 (39)	6 (42.8)	158 (39.1)	1.472 (0.288-7.532)	0.643
Anuria	1 (0.3)	3 (21.4)	4 (1)		
Dysuria	8 (2)	0	8 (1.9)	37882018.428 (0)	0.999

	Survivors (390) n (%)	Non-survivors (14) n (%)	Total 404 N (%)	Odds ratio (95% CI)	p-value
Bleeding					
Hematuria	62 (15.9)	2 (14.3)	64 (15.8)	0.341 (0.041-2.820)	0.318
Melena	14 (3.6)	1 (7.1)	15 (3.7)	0.388 (0.024-6.334)	0.507
Rash	13 (3.3)	0	13 (3.2)	35955559.717 (0)	0.999
Epistaxis	11 (2.8)	1 (7.1)	12 (3)	202425073.811 (0)	0.999
Gum bleeding	6 (1.5)	0	6 (1.5)	29154852.773 (0)	0.999
Hemoptysis	2 (0.5)	0	2 (0.5)	136328615.253 (0)	0.999
Hematemesis	2 (0.5)	0	2 (0.5)	49405232.679 (0)	1.000
Pallor	1 (0.3)	1 (7.1)	2 (0.5)	0.108 (0.002-6.882)	0.294
Respiratory					
Cough	49 (12.6)	2 (14.3)	51 (12.6)	1.067 (0.124-9.161)	0.953
Dyspnea	33 (8.5)	6 (42.9)	39 (9.7)	7.88 (1.967-31.561)	0.004
Rales	11 (2.8)	1 (7.1)	12 (3)	1.138 (0.07-24.715)	0.853
Decreased breath sounds	7 (1.8)	1 (7.1)	8 (2)	2.832 (0.118-68.011)	0.521
Chest pain	6 (1.5)	0	6 (1.5)		
Wheeze	1 (0.2)	0	1 (0.2)	0.00 (0)	1.000
Cardiac					
Hypotension	41 (10.5)	3 (21.4)	44 (10.9)	0.825 (0.097-7.020)	0.861
Irregular rhythm	3 (0.7)	1 (7.1)	4 (1)	15.34 (1.106-212.85)	0.042
Murmur	2 (0.5)	1 (7.1)	3 (0.7)		
CNS					
Headache	197 (50.5)	4 (28.6)	201 (49.7)	0.346 (0.088-1.366)	0.13
Dizziness	34 (8.7)	0	34 (8.4)	48939800.749 (0)	0.998
Seizure	2 (0.5)	1 (7.1)	3 (0.7)	9834936.187 (0)	1.000
Loss of consciousness	1 (0.2)	1 (7.1)	2 (0.5)	232266429.128 (0)	0.999
Others					
Calf tenderness	296 (75.9)	11 (78.6)	307 (76)	1.071 (0.208-5.515)	0.934
Conjunctival suffusion	268 (68.7)	11 (78.6)	279 (69)	1.302 (0.277-6.113)	0.738
Presence of wound lesions	59 (15.1)	3 (21.4)	62 (15.3)	1.327 (0.277-6.351)	0.723
Retro-orbital pain	3 (0.7)	0	3 (0.7)	13709959.617 (0)	0.999

Laboratory findings

Blood count

For both survivors and non-survivors, majority presented with leukocytosis with segmenter predominance (neutrophilia of 85.9% and 78.6%, respectively), which is consistent with bacterial infection. The majority of cases had hemoglobin levels between 100 and 130 mg/dL, (64% and 49%, respectively), with only less than 10% of subjects (in either group) presenting with significant anemia (<100 mg/dL) necessitating consideration of blood transfusion. In contrast, significant thrombocytopenia (platelet count <100) is demonstrated among the majority of nonsurvivors (61.5%), whilst normal platelet count is seen mainly among survivors (51%).

Renal function and urinary findings

Both groups presented with elevated creatinine (75% survivors and 78% non-survivors) and BUN levels (76% survivors and 100% non-survivors). Pyuria (WBC >5/hpf in urine) is more commonly seen among survivors (41%) while hematuria (RBC >5/hpf in urine) is the predominant finding among nonsurvivors (67%).

Liver function

Aspartate amino transaminase (AST) was elevated by more than 200 U/L among both survivors and nonsurvivors (96% and 100%, respectively), while alanine aminotransaminase (ALT) was mostly within normal limits (74% and 80%, respectively). Total bilirubin was elevated in 66% of survivors and 100% of non-survivors. Prolonged Prothrombin time (PT) was more common among nonsurvivors (89%) than survivors (26%), and prolonged Partial thromboplastin time (PTT) were relatively uncommon to both (6.5% among non-survivors and 11% among survivors)

Electrolyte abnormalities

Both survivors and nonsurvivors presented with either hyponatremia or normal sodium levels, with hyponatremia being slightly more common (62% and 60%, respectively). A similar trend can also be seen with potassium levels; however, hypokalemia is slightly more common among survivors than nonsurvivors (50% and 40%, respectively).

Serologic tests

Serologic tests such as microscopic agglutination test (MAT) or Leptospira antigen-antibody agglutination test (LAAT) were performed in 92 cases. MAT was done in 35 which revealed positive in 30 cases. LAAT was done in 57 cases; 49 cases were positive, all of whom were survivors. MAT or LAAT were requested during hospitalization but the results were either not available in the charts or were not done.

Chest Radiography

Chest radiograph result was available in 101 cases (25%) with normal findings in 77 cases (19%). Abnormal chest x-ray findings seen include pneumonia, congestion, cardiomegaly, and hilar lymphadenopathy. Among non-survivors, only one had available chest radiograph results with findings of pulmonary edema.

Therapeutic Management

Penicillin was the most common antibiotic used in all cases of both groups (96.8%). Other cases received other beta-lactams including amoxicillin, cefuroxime, and ceftriaxone, as well as other drugs including doxycycline, ciprofloxacin, or cotrimoxazole.

One hundred thirty cases (32.2%) had oliguric renal failure on initial assessment, of which 123 (94.6%) were treated conservatively and eventually recovered. Among survivors, seven patients (5.4%)

Table 9. Laboratory Parameters of Leptospirosis Patients

	Survivors (390) n (%)	Non-survivors (14) n (%)	Total (404) N (%)
HEMATOLOGICAL			
Hemoglobin n (%)	377 (96.7)	13 (92.9)	390 (96.5)
Mean ± SD	121.6 ± 16.8	118.9 ± 14.4	121.5 ± 16.9
(range)	(58-172)	(87-159)	(58-172)
Normal (> 130 mg/dL)	99 (26.3)	3 (23.1)	102 (26.1)
> 100 – 130 mg/dL	241 (63.9)	9 (69.2)	250 (64.1)
71 – 100 mg/dL	35 (9.3)	1 (7.7)	36 (9.2)
≤ 70 mg/dL	2 (0.5)	0	2 (0.5)
WBC counts n (%)	387 (99.2)	13 (92.9)	400 (99)
Mean ± SD	10.4 ± 4.6	11.9 ± 6.6	10.4 ± 4.6
(range)	(2.1-37.8)	(1.04-27.3)	(1.04-37.8)
Normal (WBC 5-10)	166 (42.9)	3 (23.1)	169 (42.3)
Leukocytosis (WBC >10 cells/mm^3)	186 (48.1)	9 (69.2)	195 (48.8)
Leukopenia (WBC <5 cells/mm^3)	35 (9)	1 (7.7)	36 (9)
% Neutrophils n (%)	383 (98.2)	13 (92.9)	396 (98)
Mean ± SD	0.76 ± 0.14	0.77 ± 0.18	0.76 ± 0.14
(range)	(0.198-0.965)	(0.341-0.934)	(0.198-0.965)
Within normal limits (0.40-0.60)	36 (9.2)	1 (7.1)	37 (9.1)
Neutrophilia ≥ 0.60	335 (85.9)	11 (78.6)	346 (85.6)
Neutropenia (≤ 0.40)	12 (3.1)	1 (7.1)	13 (3.2)
Platelet count n (%)	375 (96.1)	13 (92.9)	388 (96)
Mean ± SD	187.8 ± 107.3	91.1 ± 76	184.6 ± 107.7
(range)	(18-680)	(9-227)	(9-680)
Normal (150-400)	190 (50.7)	4 (28.6)	194 (50)
100-150 x10^3/mm^3	94 (25.1)	1 (7.7)	95 (24.5)
< 100 x10^3/mm^3	76 (20.3)	8 (61.5)	84 (21.6)
> 400 x10^3/mm^3	15 (4)	0	15 (3.9)
RENAL FUNCTION			
Creatinine n (%)	362 (92.8)	9 (64.3)	371 (91.8)
Mean ± SD	352.8 ± 328.7	514.6 ± 301.8	356.8 ± 328.7
(range)	(1.1-1741)	(53.9-915)	1.1-1741
Normal Creatinine for age	89 (24.6)	2 (22.2)	87 (23.4)
Elevated Crea for age	273 (75.4)	7 (77.8)	280 (75.5)
BUN n (%)	356 (91.3)	9 (64.3)	365 (90.3)
Mean ± SD	23.6 ± 45.3	27.7 ± 14.6	23.7 ± 44.8
(range)	(1.5-167)	(6.6-48.9)	(1.5-167)
Normal BUN for age	87 (24.4)	0	87 (23.8)
Elevated BUN for age	269 (75.6)	9 (100)	278 (76.2)

| | Survivors (390) | Non-survivors (14) | Total (404) |

	n (%)	n (%)	N (%)
URINE			
Pyuria (wbc >5/hpf in urine)	123/298 (41.3)	1/7 (14.3)	124/305 (40.7)
Albuminuria (+1 protein in urine)	70/250 (28)	1/2 (50)	71/252 (28.2)
Hematuria (rbc >5/hpf in urine)	80/297 (26.9)	4/6 (66.7)	84/303 (27.7)
LIVER FUNCTIONS			
AST n (%)	224 (57.4)	6 (42.9)	230 (56.9)
Mean ± SD	69.5 ± 99.1	52.7 ± 37.9	69.1 ± 98
(range)	(7.15-902)	(25-126)	(7.15-902)
Within normal limit (0-40 UL)	111 (49.5)	3 (50)	114 (49.6)
> 40-200 U/L)	102 (45.5)	3 (50)	105 (45.7)
200-500 UL	8 (3.6)	0	8 (3.5)
500-1000 UL	3 (1.3)	0	3 (1.3)
ALT n (%)	227 (58.2)	5 (35.7)	232 (57.4)
Mean ± SD	59.9 ± 142.9	40.8 ± 16.8	59.5 ± 141.3
(range)	(4.4-1417)	(20-64)	(4.4-1417)
Within normal limit (0-50 UL)	169 (74.4)	4 (80)	173 (74.6)
> 50-200 U/L)	50 (22)	1 (20)	51 (22)
200-500 UL	4 (1.8)	0	4 (1.7)
500-1000 UL	2 (0.9)	0	2 (0.9)
> 1000 UL	2 (0.9)	0	2 (0.9)
Prolonged aPTT (≥54s)	10/153 (6.5)	1/9 (11.1)	11/164 (6.7)
Prolonged PT (≥ 15s)	40/155 (25.8)	8/9 (88.9)	48/164 (29.3)
Elevated total bilirubin (>20umol/L)	55/84 (65.5)	3/3 (100)	58/91 (63.7)
ELECTROLYTES			
Sodium n (%)	258 (66.1)	10 (71.4)	268 (66.3)
Mean ± SD	133 ± 6.8	103.3 ± 8.6	132.9 ± 6.9
(range)	(110.8-174.9)	(112.9-140.8)	(110.8-174.9)
Normal Sodium	97 (37.6)	4 (40)	101 (25)
Hyponatremia (Na <135 mmol/L)	159 (61.6)	6 (60)	165 (40.8)
Hypernatremia (Na >150 mmol/L)	2 (0.8)	0	2 (0.5)
Potassium n (%)	262 (67.2)	10 (71.4)	272 (67.3)
Mean ± SD	3.5 ± 0.7	3.75 ± 0.83	3.5 ± 0.7
(range)	(1.6-6.7)	(2.13-5)	(1.6-6.7)
Normal potassium (3.5-5 mmol/L)	123 (46.9)	6 (60)	129 (47.4)
Hypokalemia (K <3.5 mmol/L)	130 (49.6)	4 (40)	134 (49.3)
Hyperkalemia (K >5 mmol/L)	9 (3.4)	0	9 (3.3)

Table 10.. Prevalence of abnormal laboratory data and their association with mortality

	Survivors n (%)	Non-survivors n (%)	Odds ratio (95% CI)	p-value
HEMATOLOGICAL				
Anemia (Hemoglobin ≤130 mg/dL)	278/377 (73.7)	10/13 (76.9)	1.187 (0.32 to 4.40)	0.798
Leukocytosis (WBC >10cells/mm^3)	186/387 (48)	9/13 (69.2)	2.432 (0.74 to 8.03)	0.145
Neutrophilia (%neutrophils ≥0.60)	335/383 (87.5)	11/13 (84.6)	0.79 (0.17 to 3.66)	0.304
Thrombocytopenia (PC <150x10^3/mm^3)	185/375 (49.3)	9/13 (69.2)	2.31 (0.70 to 7.63)	0.17
RENAL FUNCTIONS				
Elevated creatinine for age	273/362 (75.4)	8/9 (88.9)	2.61 (0.32 to 21.14)	0.369
Elevated BUN for age	269/356 (75.6)	9/9 (100)	2.91 (0.36 to 23.30)	0.314
URINE				
Pyuria (wbc >5/hpf in urine)	123/298 (41.3)	1/7 (14.3)	0.24 (0.03 to 1.99)	0.185
Albuminuria (+1 protein in urine)	70/250 (28)	1/2 (50)	2.57 (0.16 to 41.68)	0.506
Hematuria (rbc >5/hpf in urine)	80/297 (26.9)	4/6 (66.7)	5.43 (0.97 to 30.20)	0.054
LIVER FUNCTIONS				
Elevated ALT (≥ 50 U/L)	58/227 (25.5)	1/5 (20)	0.73 (0.08 to 6.65)	0.779
Elevated AST (≥40 U/L)	113/224 (50.4)	3/6 (50)	0.98 (0.19 to 4.97)	0.983
Prolonged aPTT (≥54s)	10/153 (6.5)	1/9 (11.1)	1.79 (0.20 to 15.74)	0.601
Prolonged PT (≥ 15s)	40/155 (25.8)	8/9 (88.9)	23 (2.79 to 189.67)	0.004
Elevated total bilirubin (>20 umol/L)	55/84 (65.5)	3/3 (100)	3.72 (0.19 to 74.49)	0.390
ELECTROLYTES				
Hyponatremia (Na ≤135 mmol/L)	159/258 (61.6)	6/10 (60)	0.93 (0.26 to 3.39)	0.917
Hypokalemia (K ≤3.5 mmol/L)	130/262 (49.6)	4/10 (40)	0.68 (0.19 to 2.45)	0.55

underwent peritoneal dialysis; no single non-survivors have had renal replacement therapy.

A total of 13 cases (three survivors and ten non-survivors) required intubation and assisted ventilation. Two cases among survivors underwent a blood transfusion. Inotropic support was required in 93% (13 cases) among nonsurvivors, and 16% (61 cases) among survivors.

Outcome

The average hospital stay for survivors was 6.8 ± 3.3 days, ranging from 1 to 40 days while the nonsurvivors were 1.8 ± 1.9 days. Eleven non-survivors (78.6%) stayed less than 24 hours in the hospital, wherein complications of leptospirosis had already set in. Three non-survivors stayed for five to six days.

Among survivors, acute kidney injury was seen in 72% of cases as a complication of leptospirosis. One case developed Weil's disease and another one had episodes of seizure during hospitalization. Complications such as nosocomial infection were noted in two cases, with a history of prolonged hospital stay of between eight and 40 days. Two more cases had pleural effusion and another had co-existent varicella infection.

On the other hand, of the nonsurvivors, 64.3% (9 cases) had an oliguric renal failure. Five cases progressed to Weil's disease whilst the others died of respiratory failure secondary to acute respiratory distress syndrome (2 cases) and pulmonary

hemorrhage (2 cases). Multiple organ dysfunction syndromes were seen in three cases and disseminated intravascular coagulation in one case. The cause of death in one non-survivor was unspecified.

DISCUSSION

Though there have been several studies describing the prevalence and clinical features of leptospirosis in the Philippines, these were mostly done among adults and during outbreaks. Few studies were done regarding the impact of clinical and laboratory findings in the prognosis of leptospirosis, but these were conducted among the adult population. This was the first study of leptospirosis among Filipino children that correlates the various clinical manifestations and laboratory features that could possibly predict poor outcome with leptospirosis.

As reported in previous studies[1,7,8,9,10], patients hospitalized with leptospirosis predominantly affect males within the adolescent age group, with the condition occurring more frequently during the wet season. This is consistent with the demographic findings seen in this study. Patients were mostly males (94%) because they were more frequently exposed to the outdoor environment than females[1]. It was noted that the cities of Manila, Malabon, and Caloocan were the areas most commonly affected, most likely since these areas were prone to flooding during the rainy season. This, in turn, increases the risk of exposure to contaminated flood waters where the leptospira bacteria resides, and enter through skin abrasions, mucous membranes, and the genital tract. In this study, however, the presence of skin lesions was only observed in 15.3% of cases, suggesting that this is not the main point of entry of the bacteria in the majority of cases.

As previously stated above, the most common chief complaints noted among all cases were fever, oliguria and abdominal pain, findings which are similarly noted in the study of Enoval[10] in 2012. With regard to clinical manifestations, the most frequent finding noted in this study was fever followed by gastrointestinal symptoms (abdominal pain, vomiting, and diarrhea), calf tenderness, conjunctival suffusion, and headache, which were also similar in the studies of Alfiler, Ho, and Enoval[7,8,9,10]. The study of Santos-Ocampo showed the prominence of fever and abdominal symptoms but the conjunctival suffusion often described in other literature was not observed[7]. The study of Lopes among pediatric and adult patients also showed an abrupt onset of the clinical manifestations characterized by a combination of fever, myalgia, and headache[3]. Results of this study showed that the above presentations were common to both survivors and non-survivors with no significant difference noted between two groups. However, certain clinical findings, not mentioned above were found to be more predominant among non-survivors. These include jaundice (p-value 0.014; OR 6.293, CI 1.449-27.335), dyspnea (p-value 0.004; OR 7.88, CI 1.967-31.561) and cardiac abnormalities (p-value 0.042; OR 15.343, CI 1.106-212.853).

The most frequent abnormal laboratory findings seen in the study of Santos-Ocampo include elevated BUN (84.37%), neutrophilia (75%), proteinuria (71.85%), leukocytosis (68.75%) and pyuria (65.6%)[7]. The study of Alfiler had remarkable urinary abnormalities such as proteinuria (100%), cylinduria (91%), acute renal failure (88%) and micro/macroscopic hematuria (73%)[9]. The prominence of renal abnormalities was also seen in the study of Enoval showing hematuria (96.4%), elevated creatinine (80%), albuminuria (78%) and elevated BUN (62.5%) [10]. In this study, shift to the left of the WBC differentials or neutrophilia predominates at 87.4% followed by abnormal renal function tests such as azotemia (76.2%) and creatinemia (75.7%). Anemia was seen in 73.8% of cases in contrast to other studies with lower

frequency. These findings, however, were not found to be significantly different between survivors and non-survivors. One exception is the diagnostic finding of prolonged prothrombin time (PT), which was more commonly observed among nonsurvivors (p-value 0.004; OR 23, CI 2.79 - 189).

In this study, it was noted that Weil's disease is more common among non-survivors compared to survivors, (p-value 0.007; OR 5, CI 1.575-16.631). Inotropic support was likewise found to be more predominant among nonsurvivors (p-value 0.035; OR 62.511, CI 1.33-2949.134), although this is likely due to the fact that most cases in this group present to the hospital at the later stage of illness. This could also be the reason for the significant difference in the length of hospital stay between the two groups, wherein non-survivors were found to have lesser days of inpatient stay compared with survivors (p-value 0.000; OR 3.5, CI 2.115-5.839).

The reported mortality rate of leptospirosis in children is 0% to 12%[1]. The reported mortality rate in this study was within this limit (3.5%). In the study of Santos-Ocampo, however, the observed mortality rate was 34.37%.[7] This high variability in mortality rate may be due to the possibility that the anti-acute renal failure therapy at that time was not as comprehensive and better understood as today's therapy. A factor that can influence the severity of the disease might be the delay prior to hospital admission after the onset of the symptoms, but this study showed no difference between survivors and non-survivors in terms of the onset of symptoms to hospital admission periods.

CONCLUSION

In this 5 year, multi-center study, a total of 404 cases of leptospirosis in children were reported. Leptospirosis predominates among male and adolescent age group. The Higher occurrence was noted during the rainy season that increases possible exposure to water contaminated with leptospires through wading or swimming, especially in the city of Manila, Malabon, and Caloocan. The onset of illness prior to admission was within 5 to 7 days with an abrupt onset of fever and other non-specific symptoms.

The most common clinical findings noted in this study were fever, abdominal pain, calf tenderness, vomiting and conjunctival suffusion. Abnormal laboratory findings include neutrophilia, azotemia and creatinemia, anemia, elevated bilirubin levels and thrombocytopenia.

Significant correlations with poor outcome were found in patients with jaundice (6.3%), dyspnea (7.9%), cardiac abnormality (15.3%) and prolonged prothrombin time (23%).

RECOMMENDATIONS

Further prospective surveillance is warranted to be able to accurately identify the reliable risk factors of neurosurgical site infection and actively report these events once documented. Early pre-operative clearance and surgery are recommended to lessen nosocomial infection.

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