ORIGINAL ARTICLE

Clinical presentations and predictors of mortality for leptospirosis - A study from suburban area in Malaysia

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ABSTRACT

Introduction: Malaysia is endemic for leptospirosis with increasing incidence recorded over the years. Perak has recorded one of the highest incidence and mortality of leptospirosis since 2004.

Methods: This is a retrospective study of confirmed leptospirosis cases in Larut, Matang and Selama (LMS) district in Perak reported in 2016. The demographic, clinical presentation, laboratory result and clinical outcomes data were analysed and presented.

Results: Forty-two patients with confirmed diagnosis of leptospirosis were included into the study. Majority of patients were males and Malays. The case fatality rate was 14.3%. Patients with leptospirosis present with variable clinical presentations and are commonly seen with co-infection. Patients 70-year-old and older, have clinical presentations suggestive of organ dysfunction and require intensive care are associated with higher mortality.

Conclusion: Leptospirosis is endemic in LMS district of Perak with high incidence and case fatality rate. The clinical presentation of leptospirosis is variable. Co-infection of leptospirosis with other acute febrile illness is common. Patients presenting with symptoms and signs of organ dysfunctions or require intensive care are associated with an increased odds of death.

KEY WORDS:
Leptospirosis, Weil's disease

INTRODUCTION

Leptospirosis, also known as Weil's disease is recognised by the World Health Organization as a neglected tropical disease with significant global health burden. Globally, there is an estimated to be 1.03 million cases annually with 58,900 deaths, with Southeast Asia region having the second highest incidence after Oceania. Thus leptospirosis is the leading zoonotic cause of morbidity and mortality with the majority of its burden in tropical and the world's poorest countries.[1] However, this number may be an underestimate due to a lack of updated or reliable data in many countries. Malaysia is endemic for leptospirosis due to its geographical location at the equator and Southeast Asia with heavy rainfall especially during the monsoon season. Local data revealed that the incidence of leptospirosis in Malaysia is increasing from 1.03 cases in year 2004 to 30.2 cases per 100,000 population in year 2015.[2] The Ministry of Health Malaysia has declared leptospirosis a notifiable disease since 2010 together with publication of guidelines for its diagnosis and management as well as increased accessibility for the microscopic agglutination test.[3]

Leptospirosis is caused by the highly motile, aerobic spirochaete of the genus Leptospira. The lifecycle of Leptospira is complex that involves hundreds of species of mammals identified as reservoirs, with humans being the accidental host.[4] Modes of transmission to humans are through direct contact with animal urine, contaminated water or soil or infected animal tissue, through cuts on skin or mucous membranes. Leptospirosis was once considered as an occupational disease but its association with other important factors is equally significant. The first international outbreak of leptospirosis was reported in Malaysia in the year 2000 among athletes who swam in the Segama river in "Eco-challenge" multisport race.[5] Urbanisation, poor sanitation and sewage system, overcrowding, climate changes that leads to frequent flooding have been associated with increased incidence and frequent outbreaks of leptospirosis.[6]

Clinical manifestation of the disease is protean, ranging from self-limiting illness to severe life-threatening such as Weil's disease (jaundice, renal failure, myocarditis and bleeding), pulmonary haemorrhage and meningitis/ meningoencephalitis.[7] About 5-10% of all leptospirosis cases experience severe forms of the disease with mortality of 5-15%.[4] Due to the mild and nonspecific clinical presentations of leptospirosis plus the complicated confirmatory test, it frequently leads to the confusion with other febrile illnesses, making the diagnosis difficult.[7] In Malaysia, the Perak state has recorded one of the highest incidence and mortality of leptospirosis since 2004.[6,8]

The objective of this study was to evaluate the clinical and laboratory findings for all confirmed leptospirosis cases in the districts of Larut, Matang and Selama (LMS), in northern Perak, with the land area of 2095km^2 and population of 334,073 in 2010.[9]

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MATERIALS AND METHODS

Methodology

This is a retrospective study of confirmed leptospirosis cases from the districts of LMS, in 2016. The ethics review for this study was conducted by the Ministry of Health Medical Research Ethics Committee, with the approval number of NMRR-18-1927-41168.

Data collection

Details of patients with confirmed leptospirosis was obtained from District Health Department in LMS. The medical records of patients admitted to Taiping General Hospital (TGH) were traced from Medical Record Office. Data including demographic, clinical presentation, laboratory result and clinical outcomes were recorded. Only laboratory and imaging results on the first day of presentation were recorded for further analysis. Cases not admitted to TGH were only included for analysis for demographic data and outcome but not clinical parameters. Data analysis was performed using SPSS version 20. Non-parametric tests were used in view of the small sample size, which were also not normally distributed.

Definitions

Suspected leptospirosis case: Patient with positive rapid test that has acute febrile illness with history of exposure to water and/or environment possibly contaminated with infected urine with any of the following symptoms: headache, myalgia, arthralgia, conjunctival suffusion, meningeal irritation, anuria or oliguria and/or proteinuria, jaundice, haemorrhage, cardiac arrhythmia or failure, skin rash and gastrointestinal symptoms.

Confirmed leptospirosis case: suspected case with microscopic agglutination test (MAT) titre >1:400 or 4-fold or greater rise in titre for paired sera, positive PCR, positive culture for pathogenic leptospires and demonstration using immunohistochemical staining. Abnormal laboratory results are defined according to reference range used in the laboratory in TGH.

RESULTS

Forty-two patients with confirmed diagnosis of leptospirosis were included into the study of whom 39 patients were admitted to TGH and the other three patients to other hospitals.

Demographic

A total of 42 cases of leptospirosis was reported in 2016 with estimated incidence rate of 12.57 cases per 100,000 population. Demographic features of leptospirosis patients are summarized in Table I.

Based on occupational status, 19 (45.2%) patients were recorded without formal documented occupation, eight (19.0%) were students, six (14.2%) were workers from factory while four (9.52%) were involved in agriculture, forestry and fishery.

There were six deaths, accounting for 14.3% case fatality rate and an estimated mortality rate of 1.80 per 100,000 population. In all, 50% of fatality cases occurred in patients aged ≥70.

Clinical Presentation

Patients sought medical treatment mostly on day-5 of illness. The commonest symptom was fever (89.7%) followed by gastrointestinal symptoms namely abdominal pain, vomiting and diarrhoea. Commonest signs were tachycardia (56.4%), tachypnoea (30.8%) and jaundice (22.5%). Conjunctival suffusion and muscle tenderness which is specific to leptospirosis was reported to be uncommon upon presentation, with 2.6% and 0% respectively. Other symptoms and signs are summarised in Tables II and III.

Out of 25 patients with chest radiographs available on admission, 10 were found to have documented abnormal chest radiograph. One patient had acute respiratory distress syndrome based on clinical features, arterial blood gas and chest radiograph. There was no significant association between chest radiograph abnormality and fatality, (p=0.075, FET).

Laboratory Results

Abnormal white cell count (75.0%) with thrombocytopenia (62.5%), abnormal liver enzymes (67.5%), hyponatremia (65.0%) and raised creatinine level (50.0%) were observed. The liver enzymes derangement is at best modest with values rarely elevated more than 200IU/L. Other abnormal results are summarized in Table IV.

Management

Leptospirosis was considered in differential diagnosis in 43.6% of the patients during admission. Nearly 79.5% of the patients were diagnosed as leptospirosis upon discharge or death. Mean length of hospital stay was 4.65±7.17 days.

Almost all patients (97.4%) received antibiotics during admission with ceftriaxone being the commonest (66.7%). Two patients were given both ceftriaxone and doxycycline. Other antibiotics that were used included amoxicillin + clavulanic acid, tazobactam plus piperacillin and penicillin. Eleven patients (28.2%) required intensive care and three of whom subsequently succumbed to illness. Five patients required mechanical ventilation and vasopressor respectively. Steroid was used in four patients (three hydrocortisone and one methylprednisolone). Six patients required dialysis support.

Five patients (12.8%) had other co-infections: two with dengue fever as evidenced by positive dengue IgM, one Burkholderia pseudomallei bacteraemia and the rest Escherichia coli bacteremia. Presence of coinfection was found to have no significant association with mortality (p=0.161) but the single patient infected with both leptospirosis and melioidosis succumbed to illness.

There were significant associations between mortality due to leptospirosis with symptoms of breathlessness, GCS<15, positive lung findings, oliguria, requirement of transfusion, vasopressor, blood transfusion and ventilatory support (Table V). Multivariate logistic regression however did not identify any significant predictor variable for leptospirosis mortality.

Table I: Demography of patients with leptospirosis (n=42)

	Non-fatal leptospirosis, No. (%)	Fatal leptospirosis No. (%)	Total
Patients	36	6	42
Mean Age	37.03±22.03	57.00±25.46	
Age Group			
0-9	5 (13.9)	0 (0)	5
10-19	4 (11.1)	0 (0)	4
20-29	7 (19.5)	1 (16.7)	8
30-39	4 (11.1)	1 (16.7)	5
40-49	5 (13.9)	0 (0)	5
50-59	4 (11.1)	1 (16.7)	5
60-69	4 (11.1)	0 (0)	4
≥70	3 (8.3)	3 (49.9)	6
Gender			
Male	21 (58.3)	3 (50.0)	24
Female	15 (41.7)	3 (50.0)	18
Race			
Malay	29 (80.6)	3 (50.0)	32
Chinese	3 (8.3)	3 (50.0)	6
India	4 (11.1)	0 (0)	4

Table II: Symptoms seen in leptospirosis patients (n=39)

Symptoms	No./Percentage (%)
Fever	35 (89.7)
Vomiting	25 (64.1)
Diarrhoea	18 (46.2)
Lethargy	17 (43.6)
Abdominal pain	9 (23.1)
Icterus	8 (20.5)
Headache	8 (20.5)
Arthralgia	7 (17.9)
Breathlessness	7 (17.9)
Myalgia	6 (15.4)
Bleeding tendency	3 (7.7)
Haemoptysis	2 (5.1)
Altered consciousness	1 (2.6)

Table III: Signs seen in leptospirosis patients (n=39)

Signs	No./Percentage (%)
Tachycardia, HR>100	22 (56.4)
Tachypnoea, RR>24	12 (30.8)
Jaundice	9 (22.5)
Oliguria	8 (20.5)
Positive lung findings	7 (17.9)
Hypotension, SBP<90	5 (12.8)
Hepatomegaly	3 (7.7)
Pale	3 (7.7)
Hypoxia, SPO2 < 92% RA	3 (7.7)
GCS<15	2 (5.0)
Edema	1 (2.6)
Conjunctival suffusion	1 (2.6)
Muscle tenderness	0 (0)
Splenomegaly	0 (0)

HR, heart rate; GCS, Glasgow coma scale; RA, room air; RR, respiratory rate; SBP, systolic blood pressure; SPO2, oxygen saturation.

DISCUSSION

The sociodemographic features of leptospirosis cases in the district of LMS showed a higher predisposition among males, albeit with lower male: female ratio, working age population and Malay ethnicity. This is consistent with the findings of other Malaysian studies.[2,6,10,11] The higher proportion of males detected may be attributed by gender-specific occupation and peri domiciliary activities.[1,12] Globally, the 20-49 age group is the most susceptible population to leptospirosis. Data from the Ministry of Health of Malaysian showed that patients aged from 25 to 60 constituted more than 50% of total leptospirosis cases in the year 2014 and 2015.[2]

Clinical presentation of leptospirosis is highly variable and may overlap with many febrile illnesses such as dengue fever, which is also prevalent in Malaysia. Fever, gastrointestinal

Table IV: Laboratory abnormalities of leptospirosis cases upon admission (n=39)

Laboratory Parameters	No.	Percentage (%)
Leukocytosis	19	48.8
Normal	10	25.6
Leukopenia	10	25.6
Thrombocytopenia	24	61.5
Raised creatinine	19	48.7
Hyponatremia	24	61.5
Hypokalemia	11	28.2
Normal	25	64.1
Hyperkalemia	3	7.7
Raised creatinine kinase	14	35.9
Hyperbilirubinemia	15	38.5
Raised AST	26	66.7
Raised ALT	13	33.3
Hypoalbuminemia	23	59.0
Reduced HCO3 -	20	51.3
pH<7.35	8	20.5

Table V: Categorical variables with significant association with leptospirosis fatality (n=39)

Parameters	Fatal leptospirosis (n=6), No.(%)	Non-fatal leptospirosis (n=33), No.(%)	p value	Odd ratio 95% Confidence interval, CI
Age ≥ 70	3 (50.0)	3 (9.1)	0.003	11.00 (1.5-80.4)
Symptoms				
Breathlessness	4 (66.7)	3 (9.1)	0.006	20.00 (2.52-158.68)
Altered consciousness	2 (33.3)	0 (0)	0.020	-
Clinical				
GCS<15	2 (33.3)	0 (0)	0.020	-
Positive lung finding	4 (66.7)	3 (9.1)	0.006	20.00 (2.52-158.68)
Oliguria	5 (83.3)	3 (9.1)	0.001	50.00 (4.30-581.29)
Treatment				
Vasopressor	4 (66.7)	1 (3.0)	0.001	64.00 (4.68-875.43)
Steroid	3 (50.0)	1 (3.0)	0.008	32.00 (2.49-411.44)
Ventilation	4 (66.7)	1 (3.0)	0.001	64.00 (4.68-875.43)
Dialysis	3 (50.0)	3 (9.1)	0.036	10.00 (1.36-73.33)
Transfusion	4 (66.7)	1 (3.0)	0.001	64.00 (4.68-875.43)

symptoms and body ache are common in leptospirosis and not specific. Clinical signs such as conjunctival suffusion and muscle tenderness most notably at the calf and lumbar areas are believed to be suggestive of leptospirosis. However, our study shows that these two symptoms are uncommon unlike the studies conducted in Hawaii and Taiwan.[7,13,14] This finding is most likely attributed to lack of awareness among health care workers as documentation of these signs in medical records was lacking. Our study found 79.5% of confirmed leptospirosis cases were diagnosed upon discharge or death. Misdiagnosis is common in leptospirosis. A concordant finding was seen in a cross-sectional study done in North-eastern peninsular Malaysia in which only 31% of leptospirosis cases confirmed by MAT were correctly diagnosed as leptospirosis upon discharge.[15]

Various infectious diseases such as dengue, malaria, scrub typhus and malaria have been reported to coinfect with leptospirosis.[15-18] This observation is not surprising as they are endemic at the same region that share the same epidemiological risk factors. Nearly 4.1% of 268 random patients with dengue fever in between 2012-2014 from Hospital Serdang were found to be co-infected with leptospirosis.[18] Published data on leptospirosis and melioidosis co-infection is scarce. One case cohort involving four participants of a search and rescue operation of a drowned victim, which subsequently was co-infected with both leptospirosis and melioidosis, saw a high mortality of 75%.[16] Therefore, heath care workers need to be aware that coinfection is indeed common and diagnosis of any infectious disease should not preclude further investigation for other coinfection.

Renal and hepatic dysfunction with variable severity is common a finding in leptospirosis. Hypokalaemia and hyponatremia are common and this finding is attributed by the inhibition of Na+-K+-Cl- cotransporter activity of in the thick ascending limb of Henle by the outer membrane protein of Leptospira.[19] Creatinine kinase level may be useful in differentiating leptospirosis from other acute febrile illness. A study conducted in India found that raised CK of above 500U/L with leucocytosis, raised erythrocyte sedimentation rate, hyperbilirubinemia, hypoalbuminemia and raised creatinine indicate higher probability of leptospirosis versus dengue fever.[20]

Both case fatality and mortality rates for this study is high when compared to average national data. National mortality

rate as reported from Ministry of Health, Malaysia was between 0.01 to 0.31 per 100,000 population from year 2006 to 2015 as compared to our estimate of 2.09 per 100,000 population in the district of LMS.[2] Tan et al., and Benacer et al., has reported national case fatality rate between 1.47 to 2.47% during their study period as compared with ours (14.3%).[10,12]

Significant associations were found between the fatal leptospirosis cases with conditions such as breathlessness, GCS under 15, tachypnoea, positive lung findings, oliguria. This finding implies that patients presenting with signs and symptoms of organ dysfunction (renal, respiratory and central nervous system) has increased odds of dying. Requirement of ventilation, vasopressor, blood transfusion and dialysis have also been found to be significantly associated with fatality. A study in Sao Paulo, Brazil found that the age above 40, thrombocytopenia, oliguria, pulmonary involvement and raised creatinine to be independent predictors of mortality.[20] Renal dysfunction and respiratory involvement as predictors of mortality was also confirmed in a prospective study done in Khon Kaen, Thailand.[22]

CONCLUSION

Leptospirosis is endemic in the districts of LMS of Perak with high incidence and case fatality rate. The clinical presentation of leptospirosis is variable. Co-infection of leptospirosis with other acute febrile illness is common. Patients presenting with symptoms and signs of organ dysfunction or require intensive care are associated with increased risks of death.

LIMITATIONS

This is a retrospective study involving a small sample of leptospirosis cases reported in the districts of LMS, Perak in 2016 and may not be representative of the trend of leptospirosis in the state or national level. The single laboratory result on admission that was collected for the study may not be able to reflect the progression of the disease.

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REFERENCES

1. Costa F, Hagan JE, Calcagno J, Kane M, Torgerson P, Martinez-Silveira MS, et al. Global Morbidity and mortality of leptospirosis: a systematic review. PLoS Negl Trop Dis 2015; 9(9): e0003898.
2. Wahab ZA. Epidemiology and Current Situation of Leptospirosis in Malaysia: Prosiding Persidangan Kesihatan Persekitaran Pihak Berkuasa Tempatan 2015 [Local Authority's Environmental Health Convention Proceeding]. 2015; p. 1–67. [cited Jan 2018]. Available from: http://jkt.kpkt.gov.my/jkt/resources/PDF/Persidangan_2015/persidangan kesihatan/Prosiding Persidangan Kesihatan Persekitaran 2016.pdf.
3. Malaysia Director General of Health. Surat Pekeliling Ketua Pengarah Kesihatan Malaysia BIL. 06/2014, Pemberitahuan Perubahan Klasifikasi Kes Leptospirosis bagi Diagnosa [Circular from Malaysia's Director General of Health BIL 06/2014, Notification of Changes of Classification in Leptospiros]. Kementerian Kesihatan Malaysia (Malaysia Ministry of Health); 2014. [cited Jan 2018]. Available from: http://www.moh.gov.my/index.php/database_stores/store_view_page/31/254.
4. Haake DA, Levett PN. Leptospirosis in humans. Curr Top Microbiol Immunol 2015; 387: 65-97.
5. Sejvar J, Bancroft E, Winthrop K, Bettinger J, Bajani M, Bragg S, et al. Leptospirosis in "Eco-Challenge" athletes, Malaysian Borneo, 2000. Emerg Infect Dis 2003; 9(6): 702-7.
6. Garba B, Bahaman AR, Khairani-Bejo S, Zakaria Z, Mutalib AR. Retrospective Study of Leptospirosis in Malaysia. Ecohealth 2017; 14(2): 389-98.
7. World Health Organization and International Leptospirosis Society. Human Leptospirosis: Guidance for Diagnosis, Surveillance and Control. Vol. 45. 2003. 292-292. [cited Jan 2018]. Available from: http://apps.who.int/iris/bitstream/handle/10665/42667/WHO_CDS_CSR_EPH_2002.23.pdf?sequence=1.
8. Thayaparan S, Robertson ID, Fairuz A, Suut L, Abdullah MT. Leptospirosis, an emerging zoonotic disease in Malaysia. Malays J Pathol 2013; 35(2): 123-32.
9. Department of Statistics Malaysia. Current population estimates. 2017;1–80. [cited Jan 2018]. Available from: www.dosm.gov.my.
10. Benacer D, Thong KL, Min NC, Verasahib K Bin, Galloway RL, Hartskeerl RA, et al. Epidemiology of human leptospirosis in Malaysia, 2004-2012. Acta Trop. 2016; 157: 162-8.
11. Garba B, Bahaman AR, Bejo SK, Zakaria Z, Mutalib AR, Bande F. Major epidemiological factors associated with leptospirosis in Malaysia. Acta Trop 2018; 178: 242-7.
12. Tan WL, Soelar SA, Suan MAM, Hussin N, Cheah WK, Verasahib K, et al. Leptospirosis incidence and mortality in Malaysia. Southeast Asian J Trop Med Public Health 2016; 47(3): 434-40.
13. Katz AR, Ansdell VE, Effler PV, Middleton CR, Sasaki DM. Assessment of the clinical presentation and treatment of 353 cases of laboratory-confirmed Leptospirosis in Hawaii, 1974-1998. Clin Infect Dis 2001; 33(11): 1834-41.
14. Lin PC, Chi CY, Ho MW, Chen CM, Ho CM, Wang JH. Demographic and clinical features of leptospirosis: three-year experience in central Taiwan. J Microbiol Immunol Infect 2008; 41(2): 145-50.
15. Noor Rafizah AA, Aziah BD, Azwany YN, Imran MK, Rusli AM, Nazri SM, et al. Leptospirosis in northeastern Malaysia: misdiagnosed or coinfection? Int J Collab Res Intern Med Public Heal 2012; 4(7): 1419-27.
16. Hin HS, Ramalingam R, Chunn KY, Ahmad N, Ab Rahman J, Mohamed MS. Case report: Fatal co-infection-melioidosis and leptospirosis. Am J Trop Med Hyg 2012; 87(4): 737-40.
17. Rafizah AAN, Aziah BD, Azwany YN, Imran MK, Rusli AM, Nazri SM, et al. A hospital-based study on seroprevalence of leptospirosis among febrile cases in northeastern Malaysia. Int J Infect Dis 2013; 17(6): e394-7.
18. Suppiah J, Chan SY, Ng MW, Khaw YS, Ching SM, Mat-Nor LA, et al. Clinical predictors of dengue fever co-infected with leptospirosis among patients admitted for dengue fever - A pilot study. J Biomed Sci 2017; 24(1): 40.
19. Wu MS, Yang CW, Pan MJ, Chang CT, Chen YC. Reduced renal Na+-K+-Cl-co-transporter activity and inhibited NKCC2 mRNA expression by Leptospira shermani: From bed-side to bench. Nephrol Dial Transplant 2004; 19(10): 2472-9.
20. Varma MD, Vengalil S, Vallabhajosyula S, Krishnakumar PC, Vidyasagar S. Leptospirosis and dengue fever: A predictive model for early differentiation based on clinical and biochemical parameters. Trop Doct 2014; 44(2): 100-2.
21. Spichler AS, Vilaça PJ, Athanazio DA, Albuquerque JOM, Buzzar M, Castro B, et al. Predictors of lethality in severe leptospirosis in urban Brazil. Am J Trop Med Hyg 2008; 79(6): 911-4.
22. Panaphut T, Domrongkitchaiporn S, Thinkamrop B. Prognostic factors of death in leptospirosis: A prospective cohort study in Khon Kaen, Thailand. Int J Infect Dis 2002; 6(1): 52-9.