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Incidence, Mortality, Socio-Demographic Profile and Prognostic Factors of Melioidosis in Northern Malaysia, 2014-2019

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Background

Melioidosis is a common endemic across Southeast Asia, Northern Australia, India and China. It is caused by a gram-negative bacterium named Burkholderia pseudomallei, which originates in muddy water and humid soil. The infection typically takes place following the direct contact with contaminated water or soil, mainly through an open wound, inhalation or ingestion [1,2]. Infected individuals are mostly asymptomatic, even though some may show symptoms ranging from fever, skin infection, pneumonia to multi-site abscesses. If left untreated, melioidosis would eventually lead to septic shock and death [1,3]. Melioidosis can appear as an acute or chronic infection. In an acute infection, symptoms are typically present within 2 to 14 days after the incubation period [1]. Approximately 10% of the infections would progress into the chronic stage, and the symptoms could last for more than two months. However, the chronic infection is often less fatal [2,4]. Similar to many bacterial infections, the risk of melioidosis is elevated with the presence of diabetes mellitus, chronic pulmonary disease, chronic kidney disease, alcoholism, and HIV [5,6]. Melioidosis is also well known for its unique geographical distribution. It was reported to be highly prevalent in certain regions in Australia, Thailand, and Malaysia [3,7-11]. As Kedah and Perlis are the

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largest rice producers in the country [3,7], their populations are exposed to a high risk of melioidosis. Nevertheless, the information regarding the epidemiology of the disease in both states is only available up until 2011 [10]. The objectives of this study were to determine the incidence and mortality rates of melioidosis, to describe the demographic and clinical characteristics of the patients, and to identify the factors associated with the mortality in this region.

Materials and methods

This was a cross-sectional study. The data was obtained from the Melioidosis Registry, which was maintained by the Clinical Research Centre of the Sultanah Bahiyah Hospital, Alor Setar, at the time of the study. This registry captures blood-culture-confirmed melioidosis cases encountered between January 2014 and December 2019 in 3 major public hospitals, which served as referral centers for all health institutions across Kedah and Perlis states. The information of patients gathered under the registry ranged from their demographic profiles, medical history, clinical presentation of the disease, laboratory and radiological test findings, treatment to clinical outcomes.

The information regarding the population of the two states and the rural-urban classification for the locality of melioidosis cases was sought from the Department of Statistics, Malaysia. An area was regarded as urban only if it has a population larger than 10,000, and more than 60% of the adult residents worked in non-agricultural industries [11,12].

The data was analyzed using the SPSS version 20.0 (IBM, New York). The annual incidence and in-hospital mortality rates (per 100,000) were calculated using the population of Kedah and Perlis as the denominator. The socio-demographic and clinical characteristics of the patients were summarized as frequencies and percentages. The Pearson's chi-square and Fisher's exact tests were also used to determine the associations between the survival status of the patients and their characteristics. The significant level of all the statistical tests was fixed at 0.05.

Result

Incidence and Mortality rates

Table 1 shows the incidence and mortality rates of melioidosis between 2014 and 2019. The annual incidence rates of melioidosis in northern Malaysia narrowly ranged from 2.56 to 4.84 per 100 000, while the annual mortality rates fell between 0.99 and 2.25 per 100 000.

Socio-demographic characteristics

A total of 512 cases of melioidosis were reported. Table 2 shows that most patients were male (77.5%), in the age group of 41-60 years (48.2%), of Malay ethnicity (88.7%) and from rural areas (69.1%). Age-group (*p*-value=<0.001) and occupation (*p*-value=0.007) of the patients were found to be significantly associated with their survival status. Deaths mainly occurred in those who were aged between 41-60 years as well as in those working in the farming, forestry, and fishing fields.

Underlying diseases

Table 3 shows that majority of them (67.6%) had diabetes mellitus (DM), and nearly half of them lost their lives to melioidosis. However, DM, along with other co-morbidities, was not significantly associated with the survival status of the patients.

Sites of infection, presence of septic shock, and initial treatment

Table 4 shows that many patients developed pneumonia (43.4%) and septic shock (52.5%). Slightly more than half of the patients received either ceftazidime, meropenam or imipenem as the initial treatment. Septic shock (*p*-value= 0.024) and pneumonia (*p*-value= 0.001) were suggestive of a higher possibility of death, whereas timely treatment with any of the three above mentioned antibiotics would improve the survival outcomes of patients (*p*-value= <0.001).

In soft tissue abscess (12.4%), liver abscess (9.2%) and splenic abscess (10.5%), it shows the mortality was 27.0%, 29.8% and 20.4% (*p*-value= <0.001), (*p*-value= 0.009) and (*p*-value= <0.001), respectively, that were associated with the better survival status of patients. Most of the patients were also presented with an abnormal albumin level (92.0%), random blood glucose level (79.7%) and white blood count (69.5%). An abnormal albumin level (*p*-value= <0.001) and white blood count (*p*-value= <0.001) were associated with poorer survival outcomes of the patients.

Table 1: Annual incidence and mortality rates of melioidosis (per 100,000).

Year	Incidence rate	Mortality rate
2014	3.59	2.03
2015	4.39	2.13
2016	3.41	1.68
2017	4.84	2.25
2018	2.56	0.99
2019	2.75	1.27

Table 2: Social-demographic characteristics of patients and their associations with survival status.

Variable	*n* (%)	Alive (*n* = 396) *n* (%)	Dead (*n*=115) *n* (%)	X^2 statistic(*df*)	*p*-value[a]
Gender				0.07 (1)	0.790
Male	397 (77.5)	205 (51.6)	192 (48.4)		
Female	115 (22.5)	61 (53.0)	54 (47.0)		
Age-group				21.85 (4)	<0.001
1- 20 years	32 (6.26)	27 (84.4)	5 (15.6)		

21- 40 years	86 (16.8)	51 (59.3)	35 (40.7)		
41 – 60 years	247 (48.3)	124 (50.2)	123 (49.8)		
61 – 80 years	137 (26.8)	61 (44.5)	76 (55.5)		
81-100 years	9 (1.8)	2 (22.2)	7 (77.8)		
Ethnic Group				3.90 (3)	0.272
Malay	454 (88.8)	238 (52.4)	216 (47.6)		
Chinese	19 (3.7)	9 (47.4)	10 (52.6)		
Indian	28 (5.5)	11 (39.3)	17 (60.7)		
Others	11 (2.1)	8 (72.7)	3 (27.3)		
Urban-rural status				1.31 (1)	0.252
Urban	159 (33.0)	91 (57.2)	68 (42.8)		
Rural	323 (67.0)	167 (51.7)	156 (48.3)		
Occupation				15.78 (5)	0.007
Executive/Professional/Administrative	13 (2.5)	7 (53.8)	6 (46.2)		
Industrial worker	51 (10.0)	28 (54.9)	23 (45.1)		
Farming, Forestry and Fishing	280 (54.7)	138 (49.3)	142 (50.7)		
Housewife	44 (8.6)	25 (56.8)	19 (43.2)		
Student/Children	31 (6.0)	26 (83.9)	5 (16.1)		
Unemployed	93 (18.2)	42 (45.2)	51 (54.8)		

[a]Chi-square test or Fisher's test applied

Table 3: Underlying diseases of patients and their associations with survival status.

Variable	*n* (%)	Alive *n* (%)	Dead *n* (%)	X^2 statistic(*df*)	*p*-value[a]
Underlying diseases					
Diabetes Mellitus				0.27 (1)	0.606
Yes	347 (67.8)	183 (52.7)	164 (47.3)		
No	165 (32.2)	83 (50.2)	82 (49.7)		
Chronic kidney Disease				2.76 (1)	0.097
Yes	66 (12.9)	28 (42.4)	38 (57.6)		
No	446 (87.1)	238 (53.4)	208 (46.6)		
Chronic Lung Disease				1.96(1)	0.167
Yes	17 (3.3)	6 (35.3)	11 (64.7)		
No	495 (96.7)	260 (52.5)	235 (47.5)		
HIV				-	0.625
Yes	4 (0.8)	3 (75.0)	1 (25.0)		
No	508 (99.2)	263 (51.8)	245 (48.2)		

[a]Chi-square test or Fisher's test applied

Table 4: Sites of infection, presence of septic shock status, initial treatment, and Blood investigation along with their associations with survival status.

Variable	*n* (%)	Alive *n* (%)	Dead *n* (%)	X^2 statistic(*df*)	*p*-value[a]
Site of infection					
Pneumonia				11.91(1)	0.001
Yes	222 (43.4)	96(43.2)	126(56.8)		
No	290 (56.6)	170(58.6)	120(41.4)		
Soft tissue abscess				12.77(1)	<0.001
Yes	63 (12.3)	46(73.0)	17(27.0)		
No	449 (87.7)	220(49.0)	229(51.0)		
Splenic abscess				18.52(1)	<0.001
Yes	54 (10.5)	43(79.6)	11(20.4)		
No	458 (89.5)	223(48.7)	235(51.3)		
Liver abscess				6.91(1)	0.009
Yes	47 (9.2)	33(70.2)	14(29.8)		
No	465 (90.8)	233(50.1)	232(49.9)		
Septic arthritis				1.81(1)	0.179
Yes	28 (5.5)	18(64.3)	10(35.7)		
No	484 (94.5)	248(51.2)	236(48.8)		
Prostatic abscess				-	0.250
Yes	3 (0.6)	3 (100.0)	0(0.0)		
No	509 (99.4)	263 (51.7)	246(48.3)		
Brain abscess				-	0.675
Yes	5 (1.0)	2 (40.0)	3 (60.0)		
No	507 (99.0)	264(52.1)	243 (47.9)		
Septic shock				5.10(1)	0.024
Yes	269 (52.5)	127 (47.2)	142(52.8)		
No	243 (47.5)	139 (57.2)	104(42.8)		
Initial Treatment				53.76 (1)	<0.001
Ceftazidime/Meropenam/ Imipenam	259 (50.6)	176 (68.0)	83 (32.0)		
Others	253 (49.4)	90 (35.6)	163 (64.4)		
Blood investigation at presentation					
Albumin				12.71 (1)	<0.001
Normal (34-50 g/L)	41 (8.0)	31 (75.6)	10 (24.4)		
Abnormal	401 (92.0)	186 (46.4)	215 (53.6)		
Random blood sugar				0.38 (1)	0.535

Normal (4.0-8.0 mmol/L)	104 (20.3)	61 (58.7)	43 (41.3)		
Abnormal	256 (79.7)	141 (55.1)	115 (44.9)		
White blood count				20.04 (1)	<0.001
Normal (4-10^3/UL)	156 (30.5)	104 (66.7)	52 (33.3)		
Abnormal	348 (69.5)	157 (45.1)	191 (54.9)		
Hemoglobin				1.33 (1)	0.249
Normal (13-17 g/DL)	254 (49.6)	138 (54.3)	116 (45.7)		
Abnormal	250 (50.4)	123 (49.2)	127 (50.8)		

[a]Chi-square test or Fisher's test applied

Discussion

The incidence rate of melioidosis reported in this study is closer to the lower end of the range previously reported in Australia, Thailand and Malaysia (0.6-50.2 per 100,000), so was its mortality rate (3.3-8.6 per 100,000) [13-16]. This is attributable to the improved public awareness of the disease over the years. The timely care-seeking and management of the disease are also possible reasons for the lowered mortality of melioidosis. The lower incidence from this region may contributed by clinical diagnosis that not been captured by the registry and treated well at other health facilities in the region.

The characteristics of the melioidosis patients in northern Malaysia are consistent with those reported in other regions. We found that the proportions of male and Malay patients were higher [7,17], mainly due to their active involvement in rice farming and contact with contaminated soil and water [7,12]. A higher mortality rate was also reported in the patients who worked in the farming, forestry, and fishing fields, particularly those from rural areas [18,19]. Furthermore, the results showed that most patients had co-morbidities, especially diabetes mellitus. This would be expected as most of them were above 40 years of age and still had an active lifestyle [20,22].

Although melioidosis could be presented as a wide range of symptoms including chronic localized infection and acute fulminant bacteremia involving multiple organs, acute pulmonary infection remains the most commonly reported symptom [23,24]. With or without lung abscess, pneumonia typically signals the highest risk of mortality [5,23,25]. A similar trend is demonstrated in this study [26-28]. We also found that more than half of the patients presenting with an abnormal albumin level and WBC eventually died of the infection, similar to previous findings.

The previous studies also underline the presence of visceral abscess in melioidosis patients [29], which could be detected in either acute or chronic stage of the disease and is likely to involve multiple organs [28,30,31]. As expected, the findings also suggest that the outcome of those with a single-site abscess had a better survival outcome, possibly due to their better response to the treatment. A 20 years prospective study done in Australia reported that 50% of patients who developed with septic shock succumbed from this disease [32] and presence of septic shock is one of the main predictor for mortality [33]. We found that more than 50% of the patients presented with septic shock with 52.8% mortality. In patient who presented with multiple kidney abscess, the mortality was higher and this consistence with the a study reported that in multiple kidney abscess, the mortality was 72.3% from total cases [31].

Another noteworthy finding from this study is that the patients who were treated timely with the first-line antibiotic as recommended in the Clinical Practice Guidelines, [34] either ceftazidime, meropenam and imipenam, ended up with a better survival outcome. Apart from the ceftazidime discovered as an effective treatment back in 1986, *Burkholderia pseudomallei* is susceptible to wider-range of *B*-lactam antibiotics, such as meropenem, amoxicillin/ clavulanate, ceftriaxone and cefotaxime [35].

As melioidosis cases captured by the registry were mainly those referred from other health institutions, the evaluation of the impact of delayed presentation of patients for treatment on their clinical outcomes is not feasible. Furthermore, underreporting of melioidosis cases was likely. It is noteworthy that the enrolment of patients in the registry was based solely on the blood culture findings, and some patients could have received empirical treatment before the blood test.

Conclusion

The incidence and mortality rates in this region remained consistent in general between 2014 and 2019. The factors found to be associated with a higher mortality rate included an age between 41 and 60 years; residing in rural areas; working in the farming, forestry and fishing fields; presenting with septic shock; the presence of abnormal albumin level or WBC; and not receiving timely first-line treatment. Such findings could be useful in improving the knowledge of healthcare providers about the disease as well as their ability to recognize it and provide patients with treatment timely.

Ethical approval

This conducted study has been approve by the Medical Review and Ethic Committee (MREC) with approval number: NMRR-18-3059-44128.

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