Tropical Medicine and International Health doi:10.1111/tmi.13563

VOLUME 00 NO 00

Clinical characteristics and predictors of mortality in patients with melioidosis: the Kapit experience

Valerie Toh[1,2], Sui Poh Tee[1,3] and Shen-Han Lee[4]

1 *Department of Medicine, Kapit Hospital, Sarawak, Malaysia*
2 *Clinical Research Centre, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia*
3 *Department of Medicine, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia*
4 *Department of Otorhinolaryngology, Hospital Sultanah Bahiyah, Kedah, Malaysia*

Abstract

OBJECTIVES Melioidosis, caused by *Burkholderia pseudomallei*, is prevalent in rural areas of Malaysia. The aim of this study is to delineate the epidemiology and predictors of mortality from melioidosis in Kapit district, Sarawak.

METHODS For this retrospective study of patients with culture-confirmed melioidosis admitted to Kapit Hospital, Sarawak, Malaysia, between July 2016 and July 2019, epidemiological, clinical and microbiological data were obtained. Univariate and multivariate logistic regression analyses were used to determine predictors of mortality.

RESULTS Seventy three patients met inclusion criteria. Diabetes mellitus (28.8%) and hypertension (27.4%) were primary co-morbidities. Clinical spectrum of melioidosis ranged from bacteraemia (64.4%), pneumonia (61.6%) and internal organ abscesses (49.3%) to localised soft tissue (21.9%) and joint abscesses (6.9%). Mortality rate was 12.3%. Bacteraemia and pneumonia were significantly associated with septic shock, whereas patients with soft tissue abscesses tended to present with a milder form of melioidosis without septic shock. Septic shock, mechanical ventilation, intensive care unit admission, serum urea, creatinine, bicarbonate, albumin and aspartate transaminase were all significantly associated with increased mortality on univariate analysis (all $P < 0.05$). Multivariate analysis revealed that low serum bicarbonate ($P = 0.004$, OR 0.64, 95% CI 0.48-0.87) and albumin ($P = 0.031$, OR 0.73, 95% CI 0.54–0.97) could be associated with a higher mortality.

CONCLUSION Melioidosis remains a fatal infection and commonly presents with septic shock, in the form of bacteraemia and pneumonia. Two routine clinical parameters, serum bicarbonate and serum albumin, may have important prognostic implications in septicaemic melioidosis.

keywords *Burkholderia pseudomallei*, melioidosis, predictive value of tests, retrospective, risk factors, Sarawak

Sustainable Development Goals (SDGs): Good health and well-being

Introduction

Melioidosis, caused by *Burkholderia pseudomallei*, is a potentially life-threatening disease first described in Myanmar by Whitmore and Krishnaswami back in 1912 [1]. Although melioidosis is most commonly found in Southeast Asia and Northern Australia, recent studies suggest that it could be severely underreported in many other countries [2].

Burkholderia pseudomallei is a gram-negative environmental bacterium found in the soil and surface groundwater. The bacteria enter a host through skin inoculation after exposure to soil or water in endemic regions [3]. Inhalation of *B. pseudomallei*, another mode of transmission, is often associated with a more fulminant disease with a high mortality rate [4]. An accurate, timely diagnosis of melioidosis remains a significant challenge due to its diverse clinical presentation. This fatal disease presents with a febrile illness, ranging from pneumonia to abscess formation in various internal organs such as liver, spleen, skeletal muscle and prostate [5].

Melioidosis is prevalent in Malaysia, but the true incidence is not known [6]. It was suggested that states that are active in agriculture generally report a higher

incidence of melioidosis [7]. In Sarawak, where agriculture, logging and forestry account for the main bulk of the economy, melioidosis poses a significant threat to the livelihood of people.

Mohan et al[8] reported that Kapit, a district in the East Malaysian state of Sarawak, showed some of the highest incidence rates of melioidosis in the paediatric population (20.2 per 100 000 children) in any melioidosis-endemic region. Reports on the characterisation of melioidosis and factors associated with its mortality among the adult population are scarce. This study aims to address this gap and identify predictors of mortality in adult patients with culture-positive melioidosis. The study was conducted at Kapit Hospital, one of the three hospitals that provides medical and intensive care services to a total population of 128 900 people in the largest district of Sarawak [9].

Methods

Study design and patient cohort

This is a 3-year retrospective study of culture-confirmed melioidosis cases in Kapit Hospital between July 2016 and July 2019. We identified all patients aged 13 years and older, with the diagnosis of melioidosis from the electronic admission–discharge record. All patients with at least one specimen positive for *B. pseudomallei* were included in this study. Three patients who died from causes other than melioidosis were excluded. Written medical records were then studied to collect data on epidemiological information, co-morbidities, clinical presentations, imaging and laboratory findings on admission, as illustrated in Figure 1.

Definitions

Co-morbidities such as diabetes mellitus, hypertension, alcohol use, pulmonary tuberculosis, chronic kidney disease, HIV infection, chronic obstructive pulmonary disease, congestive heart failure, end-stage renal failure and cancer were identified based on documentation in the medical records. These co-morbidities could be diagnosed at the current admission or any previously known encounters to any healthcare facilities based on the Malaysian Clinical Practice Guidelines [10]. Bacteraemia was described as positive blood culture for *B. pseudomallei*. Septic shock was defined as persistent hypotension requiring vasopressors to maintain MAP $\geq$ 65 mmHg despite adequate volume resuscitation in the context of infection, based on the Sepsis-3 guidelines [11]. Anti-melioidosis treatment was defined as the administration of first-line antibiotics to patients with suspected melioidosis before the confirmatory result became available. In Kapit Hospital, the first-line antibiotics used were intravenous ceftazidime or intravenous meropenem. Patients who recovered from melioidosis would require long-term eradication therapy for at least 20 weeks. The most commonly used eradication therapy is oral trimethoprim-sulfamethoxazole. Oral doxycycline may be added as an adjunct depending on physician's preference and patients' tolerability to the antibiotic. Oral co-amoxiclav is used as an alternative in patients who develop side effects to trimethoprim-sulfamethoxazole.

Laboratory testing

Bacterial cultures were obtained by inoculating clinical specimens onto rich media, blood agar and/or chocolate agar and/or MacConkey agar. For blood cultures, blood sample in BD BACTEC™ (Becton, Dickinson and Company, Dun Laoghaire, Ireland) medium was incubated up to 5 days. Positive blood samples were cultured onto similar medium. Then, one pure colony was subcultured on modified Francis medium (without gentamicin) to isolate the pure colony [12]. *Burkholderia pseudomallei* was identified using the API20NE (Analytical Profile Index, Non-Enterobacteriaceae) fast identification system (bioMerieux Inc., Hazelwood, MO, USA).

Blood investigations were done for all patients upon admission. Haematological and biochemical parameters were analysed using the Nihon Kohden haematology analyser (Nihon Kohden Corporation, Tokyo, Japan) and Beckman Coulter AU480 chemistry analyser (Beckman Coulter Inc., Brea, CA, USA), respectively.

Antibiotic susceptibility testing

Isolates were tested for susceptibility to ceftazidime, gentamicin, co-amoxiclav and trimethoprim-sulfamethoxazole by disc diffusion technique. Interpretive standards for disc diffusion were based on the Clinical and Laboratory Standards Institute (CLSI) guideline for *B. pseudomallei* [13]. Susceptibility to trimethoprim-sulfamethoxazole was further tested and confirmed using ETEST® (bioMerieux Inc., Hazelwood, MO, USA). Susceptibility to doxycycline was not tested as there was no specific range to confirm its sensitivity.

Ethics

The research was approved by the Medical Research Ethics Committee and registered with the National Medical Research Registrar and the Clinical Research Centre, Ministry of Health of Malaysia (NMRR-20-2160-55727). All

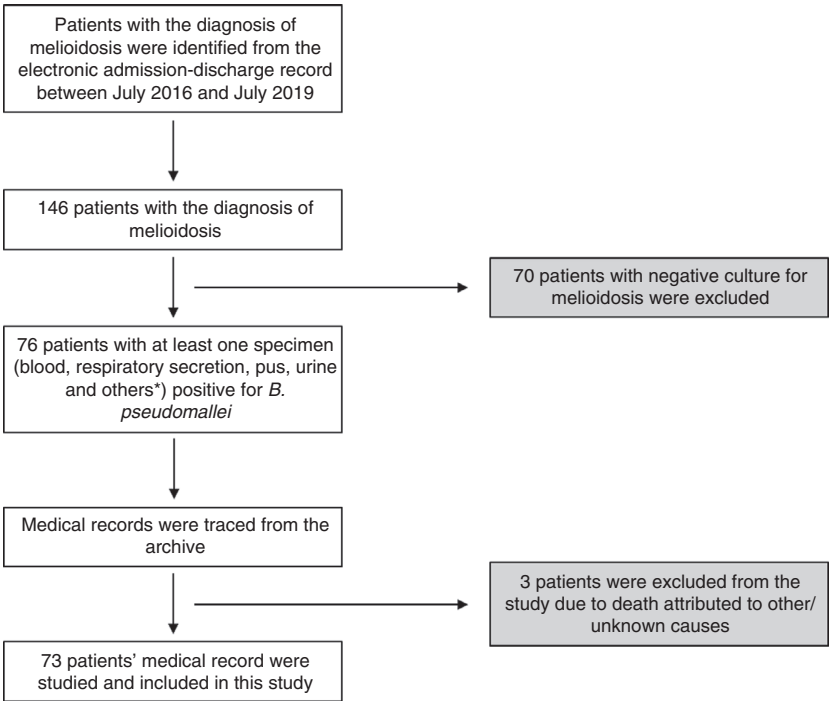

Figure 1 Graphic representation of the study design. * Others include bronchoalveolar lavage, eyelid swab, synovial fluid, urethral swab and high vaginal swab.

data were derived from medical records, and a waiver of consent was obtained from the ethics committee.

Statistical analysis

All statistical analyses were performed using SPSS Version 23 (SPSS Inc, Chicago, IL). Chi-square test was used to explore the relationship between categorical variables (patients' characteristics and clinical presentations) and septic shock and patients' outcomes. Student's t-test was used to identify the association between continuous variables (blood investigations) and septic shock and patients' outcome. A *P*-value of <0.05 was considered statistically significant. A multivariate logistic regression analysis was then performed using the statistically significant clinical parameters as independent variables and mortality as a dependent variable.

Results

Patient cohort

A total of 146 patients admitted to Kapit Hospital from July 2016 to July 2019 received a diagnosis of melioidosis, of whom, 50% ($n = 73$) had at least one positive culture. The median age of culture-positive melioidosis patients was 45 years, with a range of 13–92 years. 51 (69.9%) were male and 57 (78.1%) were of Iban ethnicity. The majority of the 57 patients with documented occupational history were loggers (40.3%; $n = 23$) and farmers (29.8%; $n = 17$) (Table 1).

Clinical presentations

Diabetes mellitus (28.8%; $n = 21$) and hypertension (27.4%; $n = 20$) were the major co-morbidities. Six of the 21 patients with diabetes mellitus were newly diagnosed during admission. Other co-morbidities were alcohol use disorder (16.4%; $n = 12$), previous history of melioidosis (9.6%, $n = 7$), pulmonary tuberculosis (6.8%; $n = 5$), chronic kidney disease (5.5%; $n = 4$), HIV infection (2.7%; $n = 2$) and chronic obstructive pulmonary disease (1.4%; $n = 1$). None of these co-morbidities were significantly associated with septic shock or an increased mortality of melioidosis. Interestingly, almost half of our culture-confirmed melioidosis patients had no co-morbidities (42.5%; $n = 31$) (Table 1).

Table 1 Epidemiology and co-morbidities of culture-proven melioidosis patients in Kapit Hospital between July 2016 and July 2019

Variables	Frequency, *n* (%); *N* = 73
Age group (years)	
≤30	24 (32.9)
31–60	37 (50.7)
>60	12 (16.4)
Gender	
Male	51 (69.9)
Female	22 (30.1)
Occupation	
Logging camp worker	23 (40.3)
Farmer	17 (29.8)
Unemployed	11 (19.3)
Others	6 (10.5)
Co-morbidities†	
Diabetes mellitus	21 (28.8)
Hypertension	20 (27.4)
Alcohol use	12 (16.4)
Previous history of melioidosis	7 (9.6)
Pulmonary tuberculosis	5 (6.8)
Chronic kidney disease	4 (5.5)
Human immunodeficiency virus infection	2 (2.7)
Chronic obstructive pulmonary disease	1 (1.4)
Congestive heart failure	0
End-stage renal failure	0
Cancer	0
No co-morbidity	31 (46.6)

†Some patients have more than one co-morbid condition.

The clinical spectrum of melioidosis presented at Kapit Hospital varied from a simple bacteraemia with no evident focus of infection to septic shock and multiorgan failure. The 28-day mortality was 12.3% ($n = 9$). Three cases were excluded from the study as they died from causes other than melioidosis. The first patient died from an exacerbation of chronic obstructive pulmonary disease (COPD) after he completed his anti-melioidosis treatment during the same admission. The other 2 patients were discharged well but subsequently brought in dead to the emergency department. The cause of death for these 2 patients was not known. As illustrated in Table 2, the majority of patients presented with bacteraemia (64.4%), followed by pneumonia (61.6%), internal organ abscesses (49.3%), soft tissue abscesses (21.9%) and septic arthritis (6.8%). There were cases of rare clinical manifestations of melioidosis, such as ocular (4.1%) (previously published as case series) [14] and central nervous system (1.4%) involvement. 39.7% required intensive care unit admission. 35.6% of patients had septic shock requiring vasopressor support and 31.5% were put on mechanical ventilation (Table 2).

Table 2 Clinical presentation and outcome for culture-positive melioidosis patients in Kapit Hospital between July 2016 and July 2019

Variables	Frequency, *n* (%); *N* = 73
Clinical presentations†	
Bacteraemia	47 (64.4)
Pneumonia	45 (61.6)
Internal organ abscesses	36 (49.3)
Soft tissue abscesses	16 (21.9)
Septic arthritis	5 (6.8)
Ocular	3 (4.1)
Neurological	1 (1.4)
Required intensive care unit admission	29 (39.7)
Required vasopressor support	26 (35.6)
Required ventilatory support	23 (31.5)
Patients' outcome	
Alive	64 (87.7)
Dead	9 (12.3)

†Some patients have more than one clinical presentation.

Table 3 Isolates of *B. pseudomallei* from various clinical specimens and its sensitivity tests in Kapit Hospital between July 2016 and July 2019

Variables	Frequency, *n* (%); *N* = 73
Types of positive culture†	
Blood	43 (58.9)
Respiratory secretion (Sputum/ETT)	21 (28.8)
Pus	11 (15.1)
Urine	4 (5.5)
Others†	10 (13.7)
Antibiotic sensitivity pattern of *B. pseudomallei*	
Ceftazidime	100%
Amoxicillin-clavulanic acid	94%
Gentamicin	92%
Trimethoprim-sulfamethoxazole	64%
Average days from first day of admission to initiation of anti-melioidosis treatment	
Minimum	1 day
Maximum	15 days
Mean	2.6 ± 2.3 days

†Some patients have more than one positive culture.
‡Others include bronchoalveolar lavage, eyelid swab, synovial fluid, urethral swab and high vaginal swab.

Table 4 Factors associated with septic shock in patients with culture-confirmed melioidosis

Variables	Septic shock (N = 26) Frequency, n (%)	Non-septic shock (N = 47) Frequency, n (%)	P-value
Age group (years)			
≤30	5 (19.2)	19 (40.4)	0.07
31–60	17 (65.4)	20 (42.6)	0.05
>60	4 (15.4)	8 (17.0)	1.00
Gender			
Male	16 (61.5)	35 (74.5)	0.25
Female	10 (38.5)	12 (25.5)	
Clinical presentations			
Bacteraemia	23 (88.5)	24 (51.1)	0.001***
Pneumonia	21 (80.8)	24 (51.1)	0.01**
Internal organ abscesses	12 (46.2)	24 (51.1)	0.37
Soft tissue abscesses†	0	16 (34.0)	0.01**
Septic arthritis	1 (3.8)	4 (8.5)	0.65
Ocular	2 (7.7)	1 (2.1)	0.29
Neurological	1 (3.8)	0	1.00
Required intensive care unit admission	23 (88.5)	6 (12.8)	<0.001***
Required ventilatory support	21 (80.8)	2 (4.3)	<0.001***
Blood investigations (normal values)			
pH (7.35–7.45)	7.45	7.45	0.82
Bicarbonate (22–26 mmol/l)	18.7	21.2	0.01**
Haemoglobin (12–15 g/dl)	12.4	12.3	0.87
Total white cells (4–10 × 10^3/ul)	15.7	12.0	0.03*
Platelets (150–400 ×10^3/ul)	228.6	354.0	0.001***
Sodium (135–145 mmol/l)	122.9	129.0	0.001***
Potassium (3.5–5 mmol/l)	3.7	3.8	0.42
Urea (2.8–8.1 mmol/l)	10.9	5.4	0.001***
Creatinine (62–106 umol/l)	211.0	101.4	0.002**
Aspartate transaminase (15–40 U/l)	170.4	92.7	0.07
Alanine transaminase (7–35 U/l)	111.7	82.4	0.31
Albumin (35–52 g/l)	32.6	34.5	0.10

†Soft tissue abscesses were found to be negatively correlated with septic shock.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$

Microbiological characteristics and treatment

The gold standard of diagnosis of melioidosis is the isolation of *B. pseudomallei* from clinical specimens. Blood (58.9%, n = 43) was the commonest source of positive culture, followed by respiratory secretions (28.8%; n = 21), pus (15.1%, n = 11) and urine (5.5%, n = 4). All identified isolates were tested for sensitivity to three commonly used antibiotics (ceftazidime, co-amoxiclav and trimethoprim-sulfamethoxazole) and gentamicin. As the *B. pseudomallei* strains in Kapit are known to be susceptible to gentamicin [15], the antibiotic is occasionally used in our local setting as an adjunct to ceftazidime. The highest sensitivity rates were recorded against ceftazidime (100%), followed by co-amoxiclav (94%), gentamicin (92%) and trimethoprim-sulfamethoxazole (64%). The mean time from admission to initiation of melioidosis antibiotics was 2.6 ± 2.3 days. 31 (42.5%) patients received appropriate melioidosis treatment on the first day of admission (Table 3).

Patients' outcome

Patients with culture-positive melioidosis who developed septic shock usually present with bacteraemia (88.5%, P = 0.001) and pneumonia (80.8%, P = 0.01). Patients with soft tissue abscesses (34.0%, P = 0.01) tend to have milder disease without septic shock. There was no significant correlation between internal organ abscesses, septic

Table 5 Factors associated with mortality in patients with culture-confirmed melioidosis

Variables	Alive (N = 64) Frequency, n (%)	Dead (N = 9) Frequency, n (%)	P-value
Age group (years)			
≤30	23 (35.9)	1 (11.1)	0.26
31–60	31 (48.4)	6 (66.7)	0.31
>60	10 (15.6)	2 (22.2)	0.64
Gender			
Male	48 (75.0)	3 (33.3)	0.02*
Female	16 (25.0)	6 (66.7)	
Clinical presentations			
Bacteraemia	39 (60.9)	8 (88.9)	0.15
Pneumonia	38 (59.3)	7 (77.8)	0.47
Internal organ abscesses	33 (51.6)	3 (33.3)	0.48
Soft tissue abscesses	16 (25.0)	0	0.59
Septic arthritis	5 (7.8)	0	1.00
Ocular	3 (4.7)	0	1.00
Neurological	1 (1.6)	0	1.00
Required intensive care unit admission	20 (31.3)	9 (100)	<0.001***
Required vasopressor support	17 (26.6)	9 (100)	<0.001***
Required ventilatory support	14 (21.9)	9 (100)	<0.001***
Blood investigations (normal values)			
pH (7.35–7.45)	7.46	7.41	0.13
Bicarbonate (22–26 mmol/l)	21.0	15.2	<0.001***
Haemoglobin (12–15 g/dL)	12.5	11.2	0.07
Total white cells (4–10 × 10^3/ul)	12.9	16.6	0.13
Platelets (150–400 × 10^3/ul)	317.9	244.4	0.21
Sodium (135–145 mmol/l)	127.1	125.3	0.53
Potassium (3.5–5 mmol/l)	3.7	4.0	0.19
Urea (2.8–8.1 mmol/l)	6.1	16.2	<0.001***
Creatinine (62–106 umol/l)	117.3	306.8	<0.001***
Aspartate transaminase (15–40 U/l)	105.5	237.9	0.03*
Alanine transaminase (7–35 U/l)	89.3	122.4	0.44
Albumin (35–52 g/l)	34.2	30.2	0.02*

*P < 0.05.
**P < 0.01.
***P < 0.001.

arthritis, ocular and neurological melioidosis and septic shock. Comparison of patients with and without septic shock revealed significant differences in various blood parameters such as serum bicarbonate, total white cell, platelets, serum sodium, urea and creatinine levels (Table 4).

Death from melioidosis was significantly associated with female sex, septic shock, mechanical ventilation, intensive care unit admission, lower serum bicarbonate and albumin levels and higher serum urea, creatinine and aspartate transaminase (Table 5). The above nine variables underwent multivariate logistic regression analysis, and the model indicated that lower serum bicarbonate (P = 0.004, OR 0.64, 95% CI 0.48–0.87) and albumin (P = 0.031, OR 0.73, 95% CI 0.54–0.97) could independently predict a rise in mortality in culture-proven melioidosis patients.

Discussion

From the study of 73 patients with culture-positive melioidosis, the typical melioidosis patient in Kapit would be a middle-aged male patient of Iban ethnicity. This reflects the demographics of the population in the district, as 59% comprise of people of Iban ethnicity [9]. The majority of the Iban population works in the agriculture and logging industry. These occupations involve regular contact with soil and water, hence increasing their exposure to environmental *B. pseudomallei*. These epidemiological findings of predominantly male patients involved in soil-related activities are similar to other studies done in Northern Malaysia, Thailand and India [16–18]. Diabetes mellitus was cited to be the major risk factor for melioidosis with the prevalence of 41%–79% [16–20], whereas only 28.8% of our study cohort had diabetes

mellitus. Almost half of our studied population had no comorbidities. This suggests that in our study population environmental exposure could be a main contributor to melioidosis process as compared to host factors.

Interestingly, a large proportion (92.8%) of *B. pseudomallei* cultures in Kapit are sensitive to gentamicin. This is consistent with a previous susceptibility study [15], which identified a mutation in a gene encoding a drug efflux pump as the cause of this sensitivity to gentamicin. Sia et al reported a case of successful treatment of melioidosis infective endocarditis with a combination of intravenous ceftazidime and gentamicin in Sarawak [21]. Future studies should be carried out to investigate if gentamicin can be used as an effective adjunct or alternative to ceftazidime and meropenem.

This study demonstrated that melioidosis has a broad range of clinical spectrum, ranging from a milder presentation such as soft tissue abscesses, to a more fulminant variant, associated with bacteraemia and pneumonia. Bacteraemia and pneumonia are the most common manifestations among culture-confirmed melioidosis patients, responsible for about 60% of our cases. This is consistent with other studies done in Northern Malaysia, Thailand, India and Singapore [16–18,20]. About half of our patients (49.3%) with melioidosis had internal organ abscesses. This percentage is considerably higher than the 7%–22% in other study cohorts [16–18,20]. Hence, bedside ultrasound scan in the acute setting may be helpful in the early detection of melioidosis [22]. We also observed that patients with septic shock tend to develop acute kidney injury, as there were significant differences in serum bicarbonate, urea and creatinine levels.

Our study recorded a mortality of 12.3%, which was considerably lower than in other centres in Malaysia, such as Kelantan (33%) [23], Kedah (34%) [24] and Johor (47.7%) [25]. It is also much lower than in other endemic regions such as Thailand (35%) [26] and India (17%) [18]. A Singaporean tertiary hospital reported a melioidosis mortality rate of 20.9% and the time from admission to initiation of antibiotics to be 6.8 $\pm$ 9.1 days [27]. Other areas in Malaysia, such as Johor, Perak and Pahang, reported that only 15.6%, 28.9% and 51.9% of melioidosis patients were given appropriate antibiotics, respectively [16,25,28]. In Kapit Hospital, physicians have a high index of clinical suspicion for melioidosis due to its prevalence in the region. The initial choice of empirical antibiotics for serious febrile illnesses were C-penicillin and ceftazidime. Bedside ultrasound scans were routinely performed in casualty for early identification of liver or splenic abscesses to confirm the clinical suspicion of melioidosis [22]. We believe that the synergistic effect of early detection of melioidosis with bedside abdominal ultrasonography and initiation of melioidosis antibiotics may be the main reason for the low mortality rate at our centre. We acknowledge that this treatment strategy may result in overuse of ceftazidime or meropenem.

Multivariate logistic regression analysis showed serum bicarbonate and serum albumin to be independent predictors of mortality. In a previous study, serum bicarbonate, but not serum albumin, was found to be a significant predictor of mortality for melioidosis [19]. Other factors such as age, female sex, pneumonia, serum urea, serum creatinine and serum bilirubin were not independently predictive of mortality in our study population. Serum bicarbonate and serum albumin have been suggested to have prognostic implications among patients in medical intensive care units [29,30].

The limitation of this study is its single-centred, retrospective nature. We have described the observed clinical features in our patients, but the reasons for these observations can only be postulated. Since the analyses were done retrospectively on culture-positive patients, the true number of melioidosis cases may be higher. There could be fatalities due to melioidosis that were not picked up in this study due to the lack of positive cultures. Despite these caveats, our study provides evidence to justify future prospective cohort studies in other endemic areas around the region. With a more comprehensive set of data across different centres, we can validate these clinical predictors of mortality and develop an early warning scoring system based on epidemiological, clinical characteristics and easily available blood parameters to identify patients requiring higher level of care and monitor treatment efficacy. It would be interesting to investigate if correction of these two biochemical parameters translates into reduction of mortality.

In summary, we have reported the clinical characteristics and factors influencing mortality in patients with culture-positive melioidosis over a 3-year period at a single centre in Kapit, Sarawak. Bacteraemia and pneumonia were significantly associated with septic shock, whereas soft tissue abscesses tend to present a milder form of the disease without septic shock. Low serum bicarbonate and albumin were independent predictors of mortality. The predictive value of these clinical parameters warrants further validation in a larger cohort of patients.

Acknowledgement

We would like to thank the Director-General of Health Malaysia for granting the permission to publish this study. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References

1. Whitmore A, Krishnaswami CS. A hitherto undescribed infective disease in Rangoon. *Ind Med Gaz [Internet]* 1912: **47**: 262–267.(Available from: http://www.ncbi.nlm.nih.gov/pubmed/29005374%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5168169).
2. Limmathurotsakul D, Golding N, Dance DAB *et al*. Predicted global distribution of Burkholderia pseudomallei and burden of melioidosis. *Nat Microbiol* 2016: **1**: 1–13.
3. Kaestli M, Schmid M, Mayo M *et al*. Out of the ground: aerial and exotic habitats of the melioidosis bacterium Burkholderia pseudomallei in grasses in Australia. *Environ Microbiol* 2012: **14**: 2058–2070.
4. Currie BJ, Fisher DA, Howard DM *et al*. Endemic melioidosis in tropical northern Australia: a 10-year prospective study and review of the literature. *Clin Infect Dis* 2000: **31**: 981–986.
5. White NJ. Melioidosis. *Lancet* 2003: **361**: 1715–1722.
6. Melioidosis - Databases [Internet]. (Available from: https://www.melioidosis.info/info.aspx?pageID=107) [28 Oct 2020]
7. Kingsley PV, Leader M, Nagodawithana NS, Tipre M, Sathiakumar N. Melioidosis in Malaysia: a review of case reports. *PLoS Negl Trop Dis* 2016: **10**: 1–18.
8. Mohan A, Podin Y, Tai N *et al*. Pediatric melioidosis in Sarawak, Malaysia: epidemiological, clinical and microbiological characteristics. *PLoS Negl Trop Dis* 2017: **11**: 1–16.
9. Department of Statistics M. Sarawak Population by District 2017.
10. Academy of Medicine of Malaysia. Malaysian clinical practice guidelines [Internet]. (Available from: http://www.acadmed.org.my/index.cfm?menuid=67) [20 Dec 2020]
11. Singer M, Deutschman CS, Seymour C *et al*. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA - J Am Med Assoc* 2016: **315**: 801–810.
12. Francis A, Aiyar S, Yean CY, Naing L, Ravichandran M. An improved selective and differential medium for the isolation of Burkholderia pseudomallei from clinical specimens. *Diagn Microbiol Infect Dis* 2006: **55**: 95–99.
13. Dolinsky AL. M100 performance standards for antimicrobial susceptibility testing [Internet]. *J Serv Mark*. 2020; **8**: 27–39.(Available from: http://www.emeraldinsight.com/doi/10.1108/08876049410065598).
14. Chang CY. Periorbital cellulitis and eyelid abscess as ocular manifestations of melioidosis: a report of three cases in Sarawak, Malaysian Borneo. *IDCases* 2020: **19**: e00683.
15. Podin Y, Sarovich DS, Price EP *et al*. Burkholderia pseudomallei isolates from sarawak, malaysian borneo, are predominantly susceptible to aminoglycosides and macrolides. *Antimicrob Agents Chemother* 2014: **58**: 162–166.
16. Tang RY, Lim SH, Lam JE, Salim N, Toh SSE, Chan YW. A 5-year retrospective study of melioidosis cases treated in a district specialist hospital. *Med J Malaysia* 2019: **74**: 472–476.
17. Churuangsuk C, Chusri S, Hortiwakul T, Charernmak B, Silpapojakul K. Characteristics, clinical outcomes and factors influencing mortality of patients with melioidosis in southern Thailand: a 10-year retrospective study. *Asian Pac J Trop Med [Internet]* 2016: **9**: 256–260.
18. Chrispal A, Rajan SJ, Sathyendra S. The clinical profile and predictors of mortality in patients with melioidosis in South India. *Trop Doct* 2010: **40**: 36–38.
19. Cheng AC, Jacups SP, Anstey NM, Curries BJ. A proposed scoring system for predicting mortality in melioidosis. *Trans R Soc Trop Med Hyg* 2003: **97**: 577–581.
20. Chien JMF, Saffari SE, Tan AL, Tan TT. Factors affecting clinical outcomes in the management of melioidosis in Singapore: a 16-year case series. *BMC Infect Dis* 2018: **18**: 482.
21. Sia T, Podin Y, Chuah TB, Wong JS. Melioidosis: an unusual cause of infective endocarditis: a case report. *Eur Hear J - Case Rep* 2018: **2**: 1–4.
22. Mohan A, Manan K, Tan LS *et al*. Detection of spleen abscesses facilitates diagnosis of melioidosis in Malaysian children. *Int J Infect Dis [Internet]* 2020: **98**: 59–66.
23. Zueter AR, Yean CY, Abumarzouq M, Rahman ZA, Deris ZZ, Harun A. The epidemiology and clinical spectrum of melioidosis in a teaching hospital in a North-Eastern state of Malaysia: a fifteen-year review. *BMC Infect Dis [Internet]* 2016: **16**: 1–11.
24. Hassan MRA, Pani SP, Peng NP *et al*. Incidence, risk factors and clinical epidemiology of melioidosis: a complex socio-ecological emerging infectious disease in the Alor Setar region of Kedah, Malaysia. *BMC Infect Dis* 2010: **10**: 2–9.
25. Pagalavan L. Melioidosis: the Johor Bahru experience. *Med J Malaysia* 2005: **60**: 599–605.
26. Hinjoy S, Hantrakun V, Kongyu S *et al*. Melioidosis in Thailand: present and future. *Trop Med Infect Dis* 2018: **3**: 38.
27. Poh MMS, Liu JS, Chan M, Leo Y-S, Vasoo S. 423. Ten-year experience of Burkholderia pseudomallei infections in a singapore tertiary hospital. *Open Forum Infect Dis* 2018; **5**: S161.
28. How SH, Ng KH, Jamalludin AR, Shah A, Rathor Y. Melioidosis in Pahang, Malaysia. *Med J Malaysia* 2005: **60**: 606–613.
29. Yin M, Si L, Qin W *et al*. Predictive value of serum albumin level for the prognosis of severe sepsis without exogenous human albumin administration: a prospective cohort study. *J Intensive Care Med* 2018: **33**: 687–694.
30. Smith I, Kumar P, Molloy S *et al*. Base excess and lactate as prognostic indicators in acute kidney injury patients admitted to intensive care Publication Type. *Intensive Care Med [Internet]*. 2009: **27**(1): 12–13.(Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=11280677&retmode=ref&cmd=prlinks%5Cnfile:///Files/C8/C8F916E2-50E4-43D3-80CF-5E56E1BA37F9.pdf).

Corresponding Author Valerie Toh, Clinical Research Centre, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia. Tel.: +6014-699 6561; E-mail: valerietohwenting@gmail.com