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Brief Original Article

What clinical factors are associated with mortality in septicemic melioidosis? A report from an endemic area

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Abstract

Introduction: Melioidosis, caused by *Burkholderia pseudomallei*, has high mortality, particularly in its septicemic form. Data on the factors associated with mortality from melioidosis are still limited.

Methodology: All patients (≥ 15 years of age) who were positive for melioidosis by blood culture in the year 2009 were enrolled. The study was conducted at Khon Kaen Hospital, Thailand. Patients were divided into two groups: surviving and deceased. Multivariate logistic regression was used to identify factors associated with death by three models: clinical, laboratory, and combined.

Results: There were 97 patients who had blood cultures positive for melioidosis. The mortality rate was 54.17% (52 patients). The clinical presentation model found one significant factor associated with mortality from septicemic melioidosis: pulmonary presentation. Two factors were statistically significant for death as determined by the laboratory model: white blood cell count (WBC) and blood urea nitrogen (BUN) value. For the combined model, three significant factors were associated with death: pulmonary presentation, WBC, and BUN. The adjusted odds ratios (95% confidence interval) of the three factors were 10.739 (3.300–34.953), 0.930 (0.877–0.985), and 1.057 (1.028–1.087), respectively.

Conclusions: Three clinical factors associated with mortality in septicemic melioidosis were pulmonary presentation, white blood cell count, and blood urea nitrogen level. Physicians should be aware of high mortality if septicemic melioidosis patients have these clinical features. Aggressive treatment may be needed.

Key words: melioidosis; sepsis; predictors; mortality.

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Introduction

Melioidosis, caused by *Burkholderia pseudomallei*, is an emerging infectious disease. It is endemic in northeast Thailand, northern Australia, and other tropical countries [1]. The incidence rate in northeast Thailand was reported to be 21.3 cases of melioidosis per 100,000 people per year [2]. Several risk factors for this emerging infection have been reported and include male gender, diabetes, renal failure, thalassemia, alcoholism, chronic lung disease, and steroid use [3,4].

B. pseudomallei are Gram-negative bacilli organisms that can be found in soil and water. Humans may get infected by skin contamination or inhalation. This bacterium can infect several organs in humans such as the lungs, liver, spleen, kidneys, skin and soft tissue, joints, or multiple organs, or can result in a disseminated infection [3]. Due to the high virulence and disseminated infection, the mortality rate of melioidosis is high. Factors associated with mortality from melioidosis, however, have not been confirmed in previous studies.

Methodology

This study was conducted retrospectively at Khon Kaen Hospital, a tertiary care hospital in northeast Thailand in an endemic area of melioidosis. All patients (≥ 15 years of age) who were admitted and tested positive for melioidosis by blood culture in the year 2009 were enrolled. Patients with incomplete data were excluded.

Clinical data of all patients were collected and included baseline characteristics; duration of presenting symptoms; occupation; co-morbid diseases; history of smoking, alcohol drinking, or steroid use; laboratory investigations; treatment; and outcomes. Patients were categorized as surviving or deceased.

The organs involved were classified as pulmonary, abdominal, musculoskeletal, or neurological presentation. Pulmonary presentation was defined as having pulmonary infiltration determined by chest X-ray with symptoms of fever, cough, or sputum production. Abdominal presentation included having liver or splenic abscess by ultrasonography. Musculoskeletal presentation included having muscular abscess or septic joints. Neurological presentation included having neutrophilic meningitis. Melioidosis titer was tested by an indirect hemagglutination assay method (Mahidol University, Bangkok, Thailand).

Statistical analyses

Baseline and clinical characteristics of surviving and deceased groups were compared using descriptive statistics. Due to small numbers in some factors, non-parametric tests were used for the bivariate analyses. Wilcoxon rank-sum and Fisher's exact tests were applied to compare the differences in numbers and proportions between the two groups, respectively.

Univariate logistic regression analyses were applied to calculate the crude odds ratios of individual variables for mortality. All clinical variables were considered statistically significant if the p value by univariate analysis was less than 0.15, and these were included in subsequent multivariate logistic regression analyses. There were three final models by multivariate logistic regression analyses, including clinical presentation, laboratory, and combined models. The combined model was run by using significant factors from independent clinical presentation and laboratory models plus antibiotic treatment. Analytical results were presented as crude odds ratios (ORs), adjusted ORs, and 95% confidence intervals (CIs). Possible interactions were tested in the final model. The significant level for interaction was set at 0.10. The goodness of fit of the multivariate model was evaluated using Hosmer-Lemeshow statistics. All data analyses were performed with STATA software version 10.1 (College Station, Texas, USA).

This study protocol was approved by the institutional review board, Khon Kaen Hospital, based on the Declaration of Helsinki and Good Clinical Practices.

Results

During the study period, there were 97 patients who were admitted and had positive blood culture for *B. pseudomallei*. One patient was excluded due to incomplete clinical data and treatment outcome. In total, there were 96 patients for analysis, and the mortality rate was 54.17% or 52 patients.

Clinical presentations between the surviving or deceased groups were mostly comparable (Table 1). There were four different clinical features between both groups, including duration of symptoms, pulmonary presentation, abdominal presentation, and musculoskeletal presentation. Patients who died had a shorter duration of symptoms, higher proportion of

Table 1. Clinical features of patients with melioidosis who survived and died.

Factors	Survived (n = 44)	Died (n = 52)	P value
Age, years	50.73 (13.50)	55.56 (11.98)	0.051
Male gender, N	33 (75.00)	42 (80.77)	0.621
Duration of symptoms, days	10.86 (10.86)	6.35 (5.84)	0.040
Agriculture, N	18 (40.91)	16 (30.77)	0.392
Diabetes, N	28 (63.64)	26 (50.00)	0.218
Hypertension, N	3 (6.82)	9 (17.31)	0.214
Thalassemia, N	1 (2.27)	0	0.458
Renal failure, N	6 (13.64)	10 (19.23)	0.586
Liver cirrhosis, N	4 (9.09)	6 (11.54)	0.750
Coronary artery disease, N	0	2 (3.85)	0.498
Tuberculosis, N	4 (9.09)	3 (5.77)	0.699
COPD, N	1 (2.27)	6 (11.54)	0.120
Steroid use, N	7 (15.91)	7 (13.46)	0.778
Smoking, N	21 (47.73)	27 (51.92)	0.838
Alcohol consumption, N	13 (29.95)	22 (43.21)	0.210
Pulmonary presentation, N	12 (27.27)	37 (71.15)	< 0.001
Abdominal presentation, N	22 (50.00)	6 (11.54)	< 0.001
Musculoskeletal presentation, N	11 (25.00)	4 (7.69)	0.025
Neurological presentation, N	0	1 (1.92)	0.999

Data are presented as mean (standard deviation) or number (percentage); differences between groups were analyzed by either Wilcoxon rank-sum or Fisher's exact test when appropriate; COPD: chronic obstructive pulmonary disease.

pulmonary presentation, but fewer patients who died had abdominal or musculoskeletal presentation compared with those patients who survived.

In terms of laboratory results, patients who died had significantly higher levels of five laboratory values than patients who survived. These factors included blood urea nitrogen, creatinine, asparate aminotransferase (AST), alanine transaminase (ALT), and total bilirubin (Table 2). A ceftazidime-based regimen was the most commonly used one in 49 patients (23 and 26 patients who died and survived, respectively; p = 0.315) (Table 2). The duration of hospitalization in patients who died was significantly longer than in patients who survived (3.75 ± 4.29 vs. 13.39 ± 10.79 days; p < 0.001).

In multivariate logistic regression analyses, the clinical presentation model found only one significant factor associated with mortality from septicemic melioidosis: pulmonary presentation, which had an adjusted OR of 6.924 (95% CI 2.066–23.212). This model was adjusted for several factors, which are shown in Table 3. Two factors were statistically significant for death as determined by the laboratory model: white blood cell count and blood urea nitrogen value, which had adjusted ORs of 0.722 (95% CI 0.540–0.966) and 1.110 (95% CI 1.026–1.201), respectively.

For the combined model, three significant factors were associated with death: pulmonary presentation, white blood cell count, and blood urea nitrogen level. The adjusted ORs (95% CI) of the three factors were 10.739 (3.300–34.953), 0.930 (0.877–0.985), and 1.057 (1.028–1.087), respectively. Decreasing white blood cell count by 1,000 cells/mm^3 increased the chance of death by 7%, while increasing one mg/dL of blood urean nitrogen level increased the risk of death by 5.7%. No significant interactions were found in the final model. The Hosmer-Lemeshow values for clinical model, laboratory model, and combined model were 91.24 (p = 0.276), 23.67 (p = 0.943), and 84.01 (p = 0.571), respectively.

Discussion

The mortality rate in septicemic melioidosis was 54.17%, which was somewhat higher than that reported in a previous study from Chonburi (47%), another province in northeast Thailand [5]. The previous study comprised 83 patients during 2001 and 2006 with a mortality rate of 47% [5]. The study from northeast Thailand showed a mortality rate of 25% [3]. The blood culture of the previous study, however, was positive in only 58% of patients [3].

Compared with other countries, the mortality rate in this study was similar to that in a report from Singapore [6]. The mortality rate of 27 melioidosis patients who admitted to the intensive care unit was 48.1%. Other studies from Malaysia, Australia, and India had lower

Table 2. Laboratory results and initial antibiotic treatment of patients with melioidosis who survived and died.

Factors	Survived (n = 44)	Died (n = 52)	P value
Hematocrit, %	30.22 (6.56)	32.83 (7.97)	0.154
White blood cell, cells/mm^3	13,390.70 (10,195.09)	10,856.73 (9,625.90)	0.086
Neutrophils, %	83.10 (9.60)	83.93 (13.85)	0.131
Platelet, cells/mm^3	210,459.50 (139,827.40)	171,520 (120,006.50)	0.208
Blood urea nitrogen, mg/dL	25.22 (21.76)	57.40 (40.77)	< 0.001
Creatinine, mg/dL	1.70 (1.42)	4.20 (3.90)	< 0.001
AST, U/L	95.66 (84.35)	367.59 (1047.83)	0.001
ALT, U/L	64.88 (37.63)	155.12 (368.31)	0.024
Total bilirubin, mg/dL	2.02 (2.00)	3.91 (3.30)	0.002
Alkaline phosphatase, U/L	356.63 (267.95)	345.28 (331.77)	0.542
Albumin, g/dL	1.96 (0.62)	1.80 (0.37)	0.374
Melioidosis titer (1:x)	1,018.57 (2253.11)	277.27 (243.88)	0.690
Antibiotic			**0.315**
Ceftriazone based	15 (34.09)	24 (46.15)	
Ceftazidime based	26 (59.09)	23 (44.23)	
Sulperazone based	1 (2.27)	4 (7.69)	
Ciprofloxacin based	2 (4.55)	1 (1.92)	

Data are presented as mean (standard deviation) or number (percentage). Differences between groups were analyzed by either Wilcoxon rank-sum or Fisher's exact test when appropriate; AST: asparate aminotransferase; ALT: alanine transaminase.

mortality rates of 32.9%, 14%, and 9.5%, respectively [7-9]. The total numbers of patients in those studies were 85, 540, and 95 patients, respectively. The study populations among these studies were different and led to different mortality rate from those in the present study. All patients in the present study had blood culture positive for melioidosis, while all patients were admitted to the intensive care unit in the study from Singapore. The other three studies included both severe and non-severe cases and both bacteremic and non-bacteremic forms. The study from Australia showed that the mortality of bacteremic patients had a mortality rate similar to that of the present study (47%) [8]. The bacteremic form of melioidosis was a severe form and had a high mortality rate, as in the present study [7-11].

This study also showed that three factors associated with death included pulmonary presentation, blood urea nitrogen level, and white blood cell count. Pulmonary presentation had the highest adjusted OR among all predictors and was also previously reported as the most common presentation of melioidosis [12,13]. Pulmonary presentation was found in 51% of patients who had melioidosis [5,15]. Seventy-one percent of patients who died from septicemic melioidosis in this study also had pulmonary problems, while only 27.27% of patients who survived had pulmonary problems (Table 1). Patients with acute pneumonia from melioidosis had a high risk of septic shock, acute respiratory distress syndrome, and death [6,13].

White blood cell count was not statistically significant by univariate logistic analysis (Table 2). After adjustment for other factors, it was independently associated with mortality from septicemic melioidosis (Table 3; combined model). Its adjusted OR was 0.930, which indicated that lower white blood cell count was associated with mortality. Lower white blood cell count was shown to be associated with early septicemia in neonates [16]. The white blood cell count, therefore, may be related to early sepsis from melioidosis.

Organ dysfunction, particularly renal dysfunction, was the main predictor in this and in previous studies [6,14]. One organ failure increased risk of death 8.2-fold, particularly renal function [6]. Renal failure is another risk factor for melioidosis [3,4], but we found

Table 3. Factors associated with mortality in patients with melioidosis by clinical, laboratory, and combined models.

Model and factors	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Clinical model		
Age	1.031 (0.997–1.067)	1.021 (0.977–1.068)
Duration of symptoms	0.932 (0.878–0.990)	0.931 (0.863–1.006)
Male gender	1.400 (0.531–3.694)	3.344 (0.885–12.636)
Agriculture occupation	0.642 (0.277–1.489)	0.481 (0.153–1.512)
Renal failure: co-morbidity	1.508 (0.500–4.544)	1.253 (0.315–4.981)
Pulmonary presentation	**5.609 (0.648–48.509)**	**6.924 (2.066–23.212)**
Abdominal presentation	0.130 (0.046–0.367)	0.292 (0.084–1.018)
Musculoskeletal presentation	0.250 (0.073–0.853)	0.263 (0.058–1.186)
Laboratory model		
White blood cell (x1000)	0.974 (0.934–1.016)	0.722 (0.540–0.966)
Blood urea nitrogen	**1.049 (1.023–1.074)**	**1.110 (1.026–1.201)**
AST	1.007 (1.001–1.012)	1.007 (0.997–1.018)
ALT	1.010 (1.000–1.020)	0.997 (0.982–1.012)
Total bilirubin	1.343 (1.082–1.668)	1.764 (0.946–3.289)
Albumin	0.509 (0.194–1.334)	0.873 (0.052–14.741)
Melioid titer	0.999 (0.998–1.000)	0.999 (0.996–1.001)
Combined model		
Pulmonary presentation	**5.609 (0.648–48.509)**	**10.739 (3.300–34.953)**
White blood cell (x 1000)	**0.974 (0.934–1.016)**	**0.930 (0.877–0.985)**
Blood urea nitrogen	**1.049 (1.023–1.074)**	**1.057 (1.028–1.087)**
Ceftazidime treatment	0.787 (0.443–1.397)	0.897 (0.417–1.929)

Bold indicates significant factors. Unadjusted odds ratios were calculated by univariate logistic regression analysis; adjusted odds ratios were calculated by multivariate logistic regression analysis; AST: asparate aminotransferase; ALT: alanine transaminase.

that having a history of renal failure was not associated with mortality in septicemic melioidosis (Table 3; clinical model). The adjusted OR (95% CI) of history of renal failure was 1.253 (0.315–4.981). However, if patients with positive blood culture for *B. pseudomallei* had high levels of blood urea nitrogen, they had a high risk of mortality. Increasing one mg/dL of blood urea nitrogen level increased the risk of death by 5.7%. The mean blood urea nitrogen of patients who died was 57.40 mg/dL (Table 1). Therefore, the risk of death was 327.18%. Blood urea nitrogen was one factor indicating organ failure. A previous study [14] showed that renal dysfunction increases mortality rate, with an adjusted OR of 1.37 (95% CI 1.11–1.71). The adjusted OR was quite similar to that in the present study (1.057; 95% CI 1.028–1.087), as shown in Table 3.

There are several antibiotic regimens for treating septicemic melioidosis. The ceftazidime-based regimen is the first-line regimen. Approximately half of the patients in this study received ceftazidime (49/96 patients, 51.05%). However, antibiotic treatment was not an independent factor for successful treatment (Table 3; combined model). Two reasons may explain this finding. The admission duration of patients who died was very short (3.75 days), and the therapeutic effects of antibiotics may not have had time to overcome bacterial virulence. Mortality from severe melioidosis was associated with renal function but not with the types of antibiotic treatment for melioidosis, either inhibitory or bactericidal effects [14].

The present study was conducted in an endemic area. The total number of septicemic melioidosis cases was quite large in only one year of study. Clinical factors may be used as predictors for mortality from septicemic melioidosis. The results may be universal for all other endemic areas, particularly resource-limited settings, because the models comprised basic routine clinical factors.

The main strength of this study is the study population. All patients were proven to have melioidosis by blood culture, which indicates septicemic melioidosis. This study was conducted in an endemic area of melioidosis. There are some limitations in the study, including small sample size and missing data. The model by multivariate logistic regression may lead to wide CIs with small sample size, such as for pulmonary infiltration (3.300, 34.953). After tracing back, the power of pulmonary presentation with the numbers of the studied population was 99%. Therefore, the wide adjusted OR for pulmonary presentation may be due to categorical type of data.

Conclusions

Three clinical factors associated with mortality in septicemic melioidosis were pulmonary presentation, white blood cell count, and blood urea nitrogen level. Physicians should be aware of high mortality if septicemic melioidosis patients have these clinical features. Aggressive treatment may be needed.

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