ผลลัพธ์การรักษาผู้ป่วยติดเชื้อเมลิออยโดสีสในกระแสเลือดในระยะเวลา 5 ปี

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โรงพยาบาลสงขลา ตำบลพะวง อำเภอเมืองสงขลา จังหวัด สงขลา

Abstract: Clinical Outcome of Bacteremic Melioidosis: A five-year Retrospective Study

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Background: Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*. It is a disease of public health importance in Thailand and is associated with high fatality rates. Objective: to evaluate clinical outcomes, characteristics, and factors influencing mortality of the patients with bacteremic melioidosis in Songkhla Hospital. Method: A retrospective cohort study of all patients (≥15 years old) admitted to the hospital from January 2015 to December 2019 with positive blood cultures for *B. pseudomallei* was conducted. Result: A total of 81 hemoculture-confirmed *B. pseudomallei* during the study period. The ages of the patients ranged from 22 to 82 years old, with a mean of 53.27 ± 14.51 years old. At least one underlying disease was documented in 68 (84%) of the patients. Most patients (50 patients, 61.7%) were referred from community hospitals. The common site of infection was a pulmonary infection, which was found in 38% of the patients, disseminated infection in 17.3%, and bacteremia without a documented site of infection was found in 37%. The median (IQR) SOFA score was 4 (0, 9) points. The overall unfavorable outcome was found in 35 patients (43.2%), including in-hospital mortality of 26 patients (32.1%), together with withdrawal treatment for end-of-life care at home for 9 patients (11.1%). Four different factors were found to have significantly influenced the unfavorable outcomes in univariate analysis, including septic shock (68.6% VS 28.3%, $p < .001$), acute respiratory failure (80% VS 34.8%, $p < .001$), DIC (20% VS 4.3%, $p = .026$), and high SOFA score (8 VS 1.5, $p < .001$). However, none of the comparisons was significant in multivariate analysis. Conclusions: Bacteremic melioidosis has a high mortality rate, and most of the unfavorable outcomes occurred within 72 hours after presentation to the hospital. Patients with septic shock, acute respiratory failure, DIC, and high SOFA scores have significantly higher mortality in univariate analysis.

Keywords: Bacteremic melioidosis, Clinical outcome, Mortality

บทคัดย่อ

ภูมิหลัง: เมลิออยโดสีสเป็นโรคที่เกิดจากการติดเชื้อ *Burkholderia pseudomallei* ซึ่งเป็นเชื้อแบคทีเรียที่พบได้ในประเทศเขตร้อนเช่นประเทศไทย และมีอัตราการเสียชีวิตสูง วัตถุประสงค์: เพื่อศึกษาผลลัพธ์การรักษาผู้ป่วย, อาการ, อาการแสดง และปัจจัยที่ส่งผลต่อการรักษาที่ไม่ดี และการเสียชีวิตของผู้ป่วยโรคเมลิออยโดสีสกลุ่มที่มีการติดเชื้อในกระแสเลือดและได้รับการรักษาในโรงพยาบาลสงขลา วิธีการ: เป็นการศึกษาแบบย้อนหลังโดยการเก็บข้อมูลทางคลินิกของผู้ป่วยเมลิออยโดสีสกลุ่มที่มีการติดเชื้อในกระแสเลือดและได้รับการรักษาในโรงพยาบาลสงขลาตั้งแต่เดือน มกราคม พ.ศ. 2558 ถึง เดือน ธันวาคม พ.ศ. 2562 ผล: มีผู้ป่วยเมลิออยโดสีสที่พบเชื้อในกระแสเลือดจำนวน 81 ราย อายุ 22-88 ปี เฉลี่ย 53.27 ± 14.51 ปี ผู้ป่วยมีโรคประจำตัวอย่างน้อย 1 ชนิด คิดเป็นร้อยละ 84 มีผู้ป่วย 50 ราย หรือคิดเป็นร้อยละ 61.7 เป็นผู้ป่วยที่ส่งต่อมาจากโรงพยาบาลชุมชน การติดเชื้อในปอดพบได้บ่อยที่สุดคิดเป็นร้อยละ 38 และมีการติดเชื้อมากกว่า 1 ตำแหน่งคิดเป็นร้อยละ 17.3 การติดเชื้อเมลิออยในกระแสเลือดโดยไม่พบแหล่งการติดเชื้ออื่นคิดเป็นร้อยละ 37 ค่าเฉลี่ยของเกณฑ์

การประเมินอวัยวะล้มเหลวเนื่องจากภาวะติดเชื้อในกระแสเลือด (SOFA score) อยู่ที่ 4 (0, 9) ผลลัพธ์การรักษาไม่ดีคิดเป็นร้อยละ 43.2 ซึ่งประกอบด้วยอัตราการเสียชีวิตในโรงพยาบาลร้อยละ 32.1 และการปฏิเสธการรักษาเพื่อดูแลในรูปแบบประคับประคองร้อยละ 11.1.จากการวิเคราะห์ข้อมูลแบบตัวแปรเดียวพบว่ามี 4 ปัจจัยที่พบในกลุ่มผู้ป่วยเมลิออยโดสีสที่มีผลการรักษาไม่ดีแตกต่างจากกลุ่มผู้ป่วยที่รอดชีวิตอย่างมีนัยสำคัญทางสถิติ ได้แก่ กลุ่มผู้ป่วยที่มีภาวะช็อคจากการติดเชื้อในกระแสเลือดซึ่งคิดเป็นร้อยละ 68.6 เปรียบเทียบกับร้อยละ 28.3, ภาวะระบบการหายใจล้มเหลวคิดเป็นร้อยละ 80.0 เปรียบเทียบกับร้อยละ 34.8, ภาวะลิ่มเลือดแพร่กระจายในหลอดเลือด คิดเป็นร้อยละ 20 เปรียบเทียบกับร้อยละ 4.3 และการมีค่าของเกณฑ์การประเมินอวัยวะล้มเหลวเนื่องจากภาวะติดเชื้อในกระแสเลือดสูงโดยมีคะแนน 8 เปรียบเทียบกับคะแนน 1.5 ในกลุ่มผู้ป่วยที่รอดชีวิต แต่ไม่พบความสัมพันธ์ดังกล่าวเมื่อได้วิเคราะห์ข้อมูลแบบหลายตัวแปร จึงไม่สามารถแสดงให้เห็นปัจจัยที่ส่งผลต่อการเสียชีวิตที่มีนัยสำคัญทางสถิติได้ **สรุป:** โรคเมลิออยโดสีสที่มีการติดเชื้อในกระแสเลือดร่วมด้วยมีผลการรักษาที่ไม่ดีและมีอัตราการเสียชีวิตที่สูง ซึ่งผู้ป่วยส่วนใหญ่จะเสียชีวิตภายใน 72 ชั่วโมงหลังเข้ารับการรักษา ภาวะช็อคจากการติดเชื้อ ภาวะระบบหายใจล้มเหลว, ภาวะลิ่มเลือดแพร่กระจายในหลอดเลือด และการมีค่าของเกณฑ์การประเมินอวัยวะล้มเหลวเนื่องจากภาวะติดเชื้อในกระแสเลือดสูง อาจเป็นปัจจัยที่สัมพันธ์กับผลลัพธ์การรักษาที่ไม่ดี

คำสำคัญ: ติดเชื้อในกระแสเลือด เมลิออยโดสีส ผลลัพธ์การรักษา อัตราการเสียชีวิต

Introduction:

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, which is predominantly found in Southeast Asia and Northern Australia. The disease's clinical spectrum ranges from pneumonia and cutaneous infection to disseminated disease with fulminant septicemia[1]. Sepsis syndrome is common, and more than 50% of patients are bacteremic at presentation[2]. The treatment consists of 2 phases; acute phase treatment, in which parenteral antibiotics are given for at least 10 days, followed by the eradication phase which oral antibiotics are given to complete a total of 20 weeks to prevent relapse of the disease[3]. The mortality in bacteremic melioidosis ranges from 9-46 %[2, 4, 5]. A previous study from a university hospital during 2003-2014 in Southern Thailand demonstrated a mortality rate of 8.9% and defined factors influencing mortality were pneumonia, septic shock, a positive blood culture for Burkholderia pseudomallei, superimposing with nosocomial infection, and inappropriate antibiotics administration[4]. Another study from a rural area in Northern Thailand during 2009-2013 demonstrate a mortality rate of 34%[5]. The difference in mortality varies due to different hospital settings.

We conducted a retrospective cohort study to evaluate the clinical outcome of patients with bacteremic melioidosis in the setting of a provincial hospital in Songkhla hospital by retrospectively reviewing the medical record of hospitalized patients with blood culture-confirmed Burkholderia pseudomallei from January 2015 to December 2019.

Material and methods:

Study design and population

A retrospective cohort sectional study was conducted at Songkhla Provincial Hospital, which is a 508-bed secondary care hospital located in Songkhla Province in Southern Thailand. All patients (≥15 years old) who were admitted to the hospital during the period from January 2015 to December 2019 with positive blood cultures for *B. pseudomallei* were included in this study. Ethical permission was obtained from the research ethical committee of Songkhla hospital. Number 2022-MD-IN3-1056.

Data collection

The collected data included patient characteristics, previous medical illness, clinical presentation, SOFA (Sequential Organ Failure Assessment) scores within 24 hours of admission, antibiotics regimens, the average length of stay, and the patient outcome.

Bacteremia was defined by positive blood culture for *B. pseudomallei* with, or without one site of focal infection, while disseminated melioidosis was defined by positive blood cultures with at least two or more focal infections. Septic shock was described as the presence of hypotension without response to fluid replacement and associated with hypoperfusion and organ dysfunction. Appropriate antibiotics therapy was defined as a treatment with at least one agent for at least 48 h to which the isolate was susceptible *in vitro*. Empirical therapy was defined as antibiotics given before the final culture results became available. Unfavorable outcomes include dead in hospital, and withdrawal treatment was defined as non-survivor.

Statistical analysis.

The Student *t*-test was used to compare continuous variables. Categorical variables were evaluated by using the 2 test or Fisher's exact test, as appropriate. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. To identify independent predictors of mortality, variables with a *p*-value of < .05 on univariate analysis were included in a multivariate logistic regression model, and a *p*-value of < .05 was considered statistically significant.

Result

A total of 81 hemoculture-confirmed *B. pseudomallei* patients were included during the study period. The demographics and clinical characteristics of the cases are shown in Table 1. The ages of the patients ranged from 22 to 82 years, with a mean of 53.2 ± 14.5 years. Sixty-two percent were male patients. At least one underlying disease was documented in 68 (84%) patients, and the most common was diabetes mellitus which was found in 41 (50.6%) of them. Most patients, consisted of 50 cases (61.7%), were referred from community hospitals.

Table 1: Baseline characteristic of hemoculture-confirmed *Burkholderia pseudomallei* patients between January 2015-December 2019 (n = 81)

Characteristics	No of patients (%)
Age, mean ± SD.	53.3 ± 14.5
Sex (male)	62 (76.5%)
Underlying disease	68 (84.0%)
At least 1 underlying disease	
- DM	41 (50.6%)
- CKD/ESRD	10 (12.3%)
- Chronic pulmonary disease	9 (11.1%)
- Cirrhosis	7 (8.6%)
- Malignancy/HIV/immunosuppressant	6 (7.4%)
- IHD/CHF/AF	4 (4.9%)
- Thalassemia	4 (4.9%)
Refer from the community hospital	50 (61.7%)

Fever was found at initial manifestation in 71 (81.7%) bacteremic melioidosis cases. The common site of infection was pulmonary infection, which was found in 38%, followed by a localized abscess in 29.6% (14.8% were hepatosplenic abscesses) of the patients. In addition, disseminated infection in 17.3% of the patients and bacteremia without documented site of infection was found in 37%, the unfavorable outcome was not statistically significant when compared to patient with bacteremia and document site of infection (34.3% VS 39.1%, *p* = .3). Three patients were presented with cardiac arrest at the emergency department. The median (IQR) SOFA score was 4 (0, 9) points.

At least one organ failure was found in 58 (71.6%) patients, acute respiratory failure in 54%, followed by septic shock in 45.7%, acute renal failure in 27.2%, acute liver injury in 19.8%, Disseminated Intravascular Coagulation (DIC) in 11.1%, and septic encephalopathy in 7.4%. Inappropriate empirical antibiotics were documented in 64.2% of the patients, and ceftriaxone was prescribed for empirical use in 66.7%, followed by ceftazidime in 13.6%, tazocin in 9.9%, and meropenem in 4%. The overall unfavorable outcome occurred in 35 patients (43.2%), which consisted of in-hospital mortality in 26 patients (32.1%), together with withdrawal treatment for end-of-life care at home in 9 patients (11.1%). (Table 2)

Table 2: Clinical manifestation and clinical outcome of bacteremic melioidosis between January 2015-December 2019 (n = 81)

Characteristics	No of the patients (%)
Fever prior admission	71 (81.7%)
Bacteremia without source	30 (37.0%)
Pulmonary infection	31 (38.3%)
Localized organ abscess	24(15.6%)
- Hepatosplenic abscess	12 (14.8%)
- Other sites	12 (14.8%)
- Genitourinary tract	6 (7.4%)
Disseminated infection	14 (17.3%)
Complication on admission	58 (71.6%)
- Acute respiratory failure	44 (54.3%)
- Septic shock	37 (45.7%)
- Acute renal failure	22 (27.2%)
- Acute liver injury	16 (19.8%)
- DIC	9 (11.1%)
- Septic encephalopathy	6 (7.4%)
SOFA, median (IQR)	4 (0, 9)
Appropriate empirical antibiotics	
- appropriate	29 (35.8%)
- inappropriate	52 (64.2%)
Time to appropriate antibiotics (IQR)	1(0, 4.5)
Discharge status	
- Improve	35 (43.2%)
- Refer back to the community hospital	11 (13.6%)
- In-hospital dead	26 (32.1%)
- Withdrawal treatment	9 (11.1%)
Length of hospital stay, median (IQR)	10 (4, 20)

There were no significant differences in age, gender, and underlying condition between the survivors and non-survivors groups. However, four difference factors were found to have significantly influenced the mortality in univariate analysis. The factors were septic shock (68.6% VS 28.3%, $p < .001$, acute respiratory failure 80% VS 34.8%, $p < .001$, DIC (20% VS 4.3%, $p = .026$, and high SOFA score (8 VS 1.5, $p < .001$) Table 3. But, neither of them was significant in multivariate analysis. (Table 4).

Table 3 Clinical parameters between survivor and unfavorable outcomes groups among bacteremic melioidosis between January 2015-December 2019.

Factors	Survivor (n=46)	Unfavorable outcomes** (n=35)	*p*-value
Age	51.6 ± 13.7	55.46 ± 15.	.239
Sex (male)	32 (69.6%)	30 (85.7%)	.089
Underlying			
- DM (n=43)	27 (58.7%)	16 (45.7%)	.246
- CKD/ESRD (n=9)	4 (8.7%)	5 (14.3%)	.428
- COPD/Asthma (n=9)	5 (10.9%)	4 (11.4%)	.937
- Cirrhosis (n=7)	4 (8.7%)	3 (8.6%)	.984
- IHD/CHF (n=4)	2 (4.3%)	2 (5.7%)	.779
- Thalassemia (n=4)	2 (4.3%)	2 (5.7%)	.779
- Malignancy/HIV/immunosuppressant (n=6)	2 (4.3%)	4 (11.4%)	.228
Complication on admission			
- Septic shock (n=37)	13 (28.3%)	24 (68.6%)	<.001*
- Acute respiratory failure (n=44)	16 (34.8%)	28 (80%)	<.001*
- Acute renal failure (n=22)	9 (19.6%)	13 (37.1%)	.078
- DIC (n=9)	2 (4.3%)	7 (20.0%)	.026*
- Acute liver injury (n=16)	8 (17.4%)	8 (22.9%)	.540
- Septic encephalopathy (n=6)	3 (6.5%)	3 (8.6%)	.727
- SOFA	1.5 (0, 6)	8 (4, 12)	<.001*
Appropriate empirical antibiotics***			
- Appropriate (n=29)	15 (32.6%)	14 (40%)	.492
- Inappropriate (n=62)	31 (67.4%)	21 (60%)	
Time to appropriate antibiotics (day)	3 (1.5, 6)	1 (0, 5)	.197
Refer from the community hospital	27(58.7%)	23(65.7%)	.520

*Significant difference with *p*-value < .05

** Unfavorable outcomes include dead in hospital and withdrawal treatment was defined as non-survivor

***Appropriate antibiotics therapy was defined as treatment with at least one agent for at least 48 h to which the isolate was susceptible *in vitro*.

Table 4 Univariate and multivariate analysis factors influencing the unfavorable outcomes.

Factors	Univariate		Multivariate	
	OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*p*-value*
Complication on admission				
- Septic shock	5.54 (2.12, 14.46)	<.001*	2.95 (0.99, 8.75)	.051
- Acute respiratory failure	7.5 (2.69, 20.94)	<.001*	2.51 (0.69, 9.1)	.161
- DIC	5.5 (1.07, 28.39)	.042*	3.28 (0.52, 20.59)	.206
- SOFA	1.21 (1.09, 1.35)	<.001*	1.11 (0.98, 1.26)	.11

*Significant difference with *p*-value < .05

Discussion

Bacteremic melioidosis among hospitalized patients has a high mortality rate. Most patients were presented with fever, while pneumonia was found in 38%. However, the primary site of infection cannot be identified in 30% of the patients. The overall unfavorable outcome was 35 (43.2%), which included in-hospital mortality in 26 (32.1%) patients, together with withdrawal treatment for end-of-life care at home in 9 (11.1%) patients. The mortality in this retrospective study was higher than in the previous study conducted in the university hospital in Southern Thailand[4]. But the result was the same as the rural hospital in northern Thailand[5]. Fifty-one percent of the patients were documented to have an unfavorable outcome within 72 hours of admission with a high SOFA score.

Pneumonia and bacteremia were the most common sites of infection, which were found in 38% and 37% of the patients, respectively. While hepato-splenic abscesses were found in 14.8% of patients lower than in previous report in Thailand[4]. The delay in the administration of appropriate antibiotics usage against *B. pseudomallei*, which was well-established as an important risk factor for mortality[4], was not demonstrated with multivariate analysis in this study due to a low sample study size. Among patients with unfavorable outcomes, there were no significant differences in appropriate antibiotics usage when compared to survivor groups (40.0% VS 32.6%, p = 0.429). The univariate analysis demonstrated a significantly high SOFA score and 45% of them were documented dead or against advice of treatment within 72 hours of admission, which might not demonstrate the mortality benefit from appropriate antibiotics. Even in appropriate antibiotics setting, the mortality rate is still high as shown in an open, prospective, randomized, comparative treatment trial of ceftazidime and imipenem for the treatment of severe melioidosis showed an overall mortality rate of 36.9%[6]. Delayed inappropriate antimicrobial treatment was associated with an increased 30-day mortality[7, 8]. Not only appropriate antibiotics, but other supportive management for sepsis patients should also be implemented to decrease mortality in bacteremic melioidosis[9].

This study cannot demonstrate the risk factor of mortality. In the resource-limited setting, even with appropriate antibiotics, the mortality of bacteremic melioidosis is still high. The study has some limitations. Firstly, the retrospective nature of the study, in which 61% of the patients were referred from community hospitals. Secondly, some information on the clinical manifestations and laboratory tests were missing, as well as inadequate investigations such as total fluid resuscitation, urine output, hemoculture, and initial blood chemistry. Finally, the change in hospital information system made the researcher unable to collect more retrospective cases, resulting in a small sample size.

In summary, bacteremic melioidosis has a high mortality rate, and most unfavorable outcomes occur within 72 hours after presentation to the hospital. Patients with septic shock, acute renal failure, and respiratory failure have significantly higher mortality rate in a univariate analysis.

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