Review

REVIEW OF RESEARCH ON MORTALITY FROM MELIOIDOSIS IN MALAYSIA

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Abstract: Melioidosis, or Whitmore's disease, is an infectious disease initiated by a bacteria known as *Burkholderia pseudomallei*. This bacteria is commonly found in contaminated soil and water. In Malaysia, the mortality from melioidosis infection was reported to be higher than in other infectious diseases. The research on melioidosis is still limited in Malaysia but slightly increasing. The article's objective was to seek all the melioidosis research related to mortality in Malaysia. The information from the selected papers was then abstracted into two sections; Section 1: Review of literature and Section 2: Findings on mortality from melioidosis in Malaysia. In Section 1, the information on transmission and clinical features of melioidosis, demographic, severity of melioidosis, a clinical signs of melioidosis, diagnosis of melioidosis, management of melioidosis, the economic burden of melioidosis, and incidence of mortality from melioidosis were discussed in this paper. Meanwhile, in Section 2, the findings on mortality of melioidosis in Malaysia were discussed according to eight published articles. It is important to manage patients with melioidosis with appropriate treatment and management to reduce severe complications, high fatality rate, and relapse. More published research on melioidosis will provide input to the clinicians on a more detailed understanding of how to improve the diagnosis of melioidosis and the prognosis factors of this disease.

Keywords: Epidemiology; melioidosis; infectious disease; mortality; risk factors; transmission

1. Review of Literature

1.1. Transmission and Clinical Features of Melioidosis

B. pseudomallei that cause melioidosis can form a biofilm. The formation of biofilm is an important feature in bacteria's pathogenesis due to its capability to promote the survival of the bacteria or extent within the host and shield itself from antibiotics [1]. This enables *B. pseudomallei* not to affect various antibiotics, including penicillins, rifamycins, aminoglycosides, and many third-generation cephalosporins [2]. Although melioidosis is mainly transferred by inhalation, it may rarely be acquired via nosocomial infections, laboratory accidents, vertical transmission at childbirth, and sexual contact [3]. Melioidosis has the ability to assume different forms ranging from periodontal abscess to disseminated abscesses, septicemia, shock [4]–[6], and also possible death [7], [8]. Based on Currie et al., it was reported that many patients with melioidosis in Malaysia, Singapore, Thailand, and Northern Australia have a severe bloodstream infection because

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of lungs are the most common organ affected by this disease [9]. However, it is uncommon in melioidosis to involve the central nervous system [10].

1.2. Demographic

Melioidosis is an infectious disease caused by the bacteria *Burkholderia pseudomallei*. The bacteria is a natural inhabitant in the soil and freshwater. Still, the bacteria can rarely survive in dry atmospheric conditions [11]. Melioidosis can kill more people each year than common diseases like tuberculosis, leptospirosis, and dengue [12], with a mortality rate of more than 40% [13]. Despite this, melioidosis is currently not listed in the neglected tropical diseases (NTDs) by the World Health Organization (WHO) [14]. *Burkholderia pseudomallei* was categorized as a B bioterrorism agent by the Centre for Disease Control and Prevention [15]. The majority of the people with melioidosis come from low-income and middle-income states, common in Southeast Asia, Northern Australia, Africa, India, and China [14]. The disease ordinarily occurs in people aged 40 to 60 and males [11].

Melioidosis mostly affects vulnerable persons who are directly in contact with polluted wet soil [16]. The elderly with low immune systems, especially those suffering from diabetes mellitus and/or alcoholism, are at risk of developing infection [17]. A typical clinical presentation among the affected individuals is sepsis, intra-abdominal abscess, and pneumonia [18]. The disease's severity depends on how the bacteria enter the human body, the body system's immune system, and bacterial strain and load [11]. The current research proposes that the inhalation of the bacteria during the wet monsoon [19], [20] is also an indicator of infection.

The incidence of melioidosis has increased dramatically in recent decades. In Malaysia, the first cases were reported in Kuala Lumpur around 1913 [21]. The spread of the disease occurred after the Second World War in Malaysia, Thailand, and Burma, with 10 cases reported in Malaysia [10]. Since that time, the Department of Medical Microbiology at the University of Malaya was established, research and reports on the risk factors of the disease were studied and published [10]. In 1994, the First International Symposium on Melioidosis organized by the Malaysian Society of Infectious Diseases and Chemotherapy was held in Kuala Lumpur, attended by 100 participants worldwide presenting their papers on melioidosis.

The exact incidence of melioidosis in Malaysia is unidentified as it is not a notifiable disease in Malaysia, although over a thousand cases have been reported all over Malaysia [22]. Around the 1980s in Malaysia, this disease was associated with a high mortality rate in hospitals, particularly in the septicaemic form, which is 65%. With the new treatment to this patient of a high dose of ceftazidime, imipenem, or cefoperazone-sulbactam for a minimum of two weeks, the mortality rate has been reduced to 19-37% in the past 20 years [23].

Incidence may vary between states, and even within the same state, there may be various hotspots [24]. The incidence of melioidosis in Pahang, where agriculture is the main economic activity, recorded culture-confirmed adult melioidosis of 6.1 per 100,000 population per year from 2000–2003. The state of Kedah, situated at the Malaysia–

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Thailand border and is the largest rice producer in Malaysia, reported an incidence of 16.35 per 100,000 population a year [25].

Melioidosis commonly affects middle-aged patients. In a four-year retrospective study in Kedah from 2004 to 2007, involving 453 cases of adult melioidosis, the youngest was eight months old, and the oldest was 89 years old. The mean age was 51.88(15.19) years old. The same study reported the mean age of the melioidosis patient was 51.88(15.19) years old [26]. In terms of ethnic groups, the majority who were affected were Malays, followed by Chinese and Indians (Ratio of 4.1:1.5:1). When comparing the proportion of males and females in melioidosis disease, males tend to expose to the disease compared to females. This is probably due to the high-risk exposure of *B. Pseudomallei* in males while doing their job. In all studies reported in Malaysia [5, 10], the ratio of males compared to females was higher. The majority of patients were Malay since the state is dominated by the Malay population [25]–[27].

1.3. Severity of Melioidosis

The clinical classification of melioidosis is still debatable. Categorizing into acute, subacute, and chronic melioidosis or organ involvement is inadequate. According to the Infectious Disease Association of Thailand (IDAT), melioidosis was categorized into four categories; transient septicemic melioidosis, bacteremic multifocal infection with septicemia, and non-bacteremic localized infection, and bacteremic localized infection with septicemia [28]. Based on Puthucheary (2009), to be more precise, melioidosis can be classified into septicemic and non-septicemic [10].

1.4. Clinical Signs of Melioidosis

Clinical signs of melioidosis can be divided based on the form of melioidosis. The common form of melioidosis is acute pulmonary infection. At the beginning of infection, patients will have a more than 39° C fever, cough, aching chest, headache, and anorexia. During the investigation procedure, the chest usually appears with upper lobe consolidation. Patients have a normal to 20,000/mcL (20 × 109/L) range of white blood cell count [29].

It can happen in all organs in the body for a localized infection, but it is most common in the skin (or lungs) and lymph nodes related. The condition normally occurs in the liver, spleen, kidneys, prostate, bone, and skeletal muscle. Patients will have localized pain or swelling on the infection site with the presence of fever, ulceration, and abscess. In septicemic infection, patients will have fever and headache with respiratory pain, abdominal distress, and joint pain. Mortality rates are higher in bloodstream infection, where death may happen within 48 hours of admission, even with antibiotics. The same common symptoms will be found in patients with disseminated infection. Correspondingly, seizures and loss of weight happen in disseminated infection [29].

1.5. Diagnosis of Melioidosis

Several methods were applied to prevent misdiagnosis in detecting melioidosis, such as culture-based method, antigen detection, antibody detection, rapid culture techniques,

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and molecular techniques [30]. The gold standard to diagnose melioidosis is by isolating and identifying *B. pseudomallei* from the body fluids, including sputum, urine, tissues, blood samples, and wounds [30], [31]. In Malaysia, the routine practice of diagnosing the disease is blood culture tests and serology tests [2], [32]. The serology test is less reliable and biased because of high background titre levels and cross-reaction with other organisms [33]. The use of media like Francis media agar, MacConkey agar, blood agar, and chocolate agar for the culture test differs from one hospital to another. Still, all these media are the most commonly used in Malaysia's hospitals (Nathan et al., 2018). The sample will be allowed to grow in media at 37 Celsius, and validation will be done by observing the colony morphology, staining reaction, motility, and biochemical tests (How et al., 2005).

The disadvantage of using the culture test is that the method usually takes up to a week to confirm *B. pseudomallei* [33]. The range of time consumed in detecting the organism by culture test is 2 to 7 days [34]. The delayed diagnosis of melioidosis leads to the higher fatality of melioidosis until up to 50% [35]. Besides, the method also reported a low true positive rate (60%) in detecting the *B. pseudomallei* [30], [35], [36]. The method is also not readily available in certain areas since the need for experts, and strict safety should be practiced [2].

Even though serology test and direct PCR assay of a clinical sample can provide a fast test result compared to culture test, both methods are less sensitive in confirming the diagnosis of melioidosis [15]. In endemic regions, serology tests could provide a high background seropositivity rate of more than 50% [15]. Until now, the culture test is recommended for confirming B. pseudomallei.

1.6. Management of Melioidosis

There are no standardized guidelines for treating melioidosis patients in south Asian countries [37]. Pahang State Health Department published an approach for clinical and public health management of melioidosis in Pahang that is reviewed every three years [38]. The guideline is also practically applied in other states in Malaysia. The treatment of melioidosis patients is divided into general treatment and antibiotics [38].

General treatment includes balancing abnormal fluid, electrolytes, and acid-based, giving insulin therapy for diabetic patients, monitoring the pulse or arterial blood gases in older patients with necessitate respiratory support, I & D or drainage in patients with abscess, and applying regular protection measures for infection control [38].

Antibiotics used to treat melioidosis during intensive therapy are based on the type of melioidosis. For life-threatening melioidosis, IV Meropenem or IV Imipenem is used for at least two weeks with a combination of Trimethoprim-Sulphamethoxazole daily for severe and profound focal infection [39]–[41]. The granulocyte-colony stimulating factor drugs also should be considered within 72 hours of admission [42]. For localized superficial melioidosis, oral augmentin (Amoxycillin or Clavulanate) is used for 12 to 20 weeks [43]. Other than the above, IV Ceftazidime is used for at least two weeks and up to 8 weeks for deep infection [44]. For eradication therapy, trimethoprim and sulfamethoxazole are used, and the patients should be monitored for 20 weeks [40]. Also,

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patients who are allergic to Co-trimoxazole and pregnant mothers can use augmentin as an alternative [40].

1.6. Economic Burden of Melioidosis

The increase of melioidosis cases in endemic areas in Malaysia likely carries a high economic burden. The treatment for melioidosis patients requires intensive antimicrobial in the critical phase as well as prolonged eradication treatment [2]. The high number of hospitalized patients and high mortality rate due to melioidosis cause a need for expensive treatment and cost, leading to an extensive economic impact on society in terms of productivity losses [45]. Based on research performed in Thailand, the high average annual direct medical costs were associated with the cases of hospitalized bacteremic melioidosis in Sa Kaeo and Nakhon Phanom. In Sa Kaeo, the treatment amounted to $37,066 ($16,187 severe cases and $20,876 non-severe cases), while $66,993 cases ($17,178 severe cases and $47,475 non-severe cases) were reported in Nakhon [45]. Another study in Vietnam reported the cost to detect the selective culture in melioidosis was approximately $100 in Vientiane and $39 in Siem Reap per patient [46]. One reported study on the direct medical cost of melioidosis in Malaysia showed that the cost of treating melioidosis patients increased after the length of hospital stay [47].

1.7. Mortality from Melioidosis

The fatality rate reported in melioidosis patients was higher in developed countries (Inglis et al., 2003). *B. pseudomallei* is naturally resistant to many antimicrobial agents [17]. In 1932, the mortality rate reported was 98%, with 83 cases in South and Southeast Asia [11].

Based on the published report from 1975 to 2015, 67 cases were reported in Malaysia, with 43% (29 cases) mortality [48]. A study conducted in Hospital Universiti Sains Malaysia, Kubang Kerian, reported 33% mortality from 2001 to 2015 [27]. Another study conducted in Alor Setar, Kedah, also reported that the mortality rate was 34% from 2005 to 2008 [25]. How et al., 2005 reported the percentage of deaths in Kuantan, Pahang from 2000 to 2003 was 54% higher than in Kedah and Kelantan [22]. Another study in Kuala Lumpur reported a higher number of deaths among bacteremic melioidosis cases, with 65% deaths from 1976 to 1991 [48].

In Johor Bharu, the mortality rate was 47.7% from 1999 to 2003; where eight out of the 21 patients (38.1%) and 9 (42.9%) died within 24 hours of admission and died after 72 hours of admission, respectively [49]. Another mixed prospective and retrospective study that was conducted at three major hospitals in Sarawak reported a percentage of 43% of children died from melioidosis [24].

2. Findings of Mortality from Melioidosis in Malaysia

Age was found to be a prognostic factor towards mortality among melioidosis patients in this study. The relation between older age and underlying disease was reported in many published studies. The current study's finding demonstrated that every one-unit increase in age would increase 1.2% risk of mortality. A recent study among the culture-

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confirmed melioidosis patients in Thailand reported a similar result with the risk of mortality by 1% (95% CI: 1-04, 4.29) [50]. Another study documented 540 melioidosis cases over 20 years in Top End Australia reported the same result that those aged ≥ 50 years old increased the risk of dying from melioidosis by two compared to those aged < 50 years old (95% CI: 1.2, 2.3) [51]. A study in Hospital Universiti Sains Malaysia Kubang Kerian, Malaysia, reported that patients with more than 40 years old increased the chance of dying by 6.47 (95% CI: 1.7, 23.8) [27].

Lower systolic blood pressure and diastolic blood pressure were found to be protective towards mortality from melioidosis. In a case report in a patient with septicemia melioidosis, the pulse was 112/min with a blood pressure of 102/60 mmHg [52]. There were no reported odds or hazard ratios in a published study that used multivariable analysis on this factor.

Urea was also a significant prognostic factor towards mortality from melioidosis. The Cox and AFT showed a similar finding, demonstrating that increased one mmol/L of urea will increase the risk of dying from melioidosis. The logistic model result showed contradicted after the variable was transformed to adjust the linearity of the variable. Several studies showed a significant correlation between elevated urea and mortality among melioidosis patients (Cheng et al., 2003; Manimaran R, Anand S, Aravind K, 2018; Kirby et al., 2019). A study in Khon Khaen Hospital comparing the risk of clinical factors towards mortality found that increasing one unit of blood urea nitrogen level (unit in mg/dL) will increase the risk of dying from melioidosis by 5.7% (95% CI: 1.028, 1.087) [56]. A Darwin study reported a similar finding showing that every one mmol/L increased serum urea in melioidosis patients would increase the risk of dying by 3% (95% CI: 0.99, 1.07) [53].

Platelet count was one of the prognostic factors of mortality from melioidosis. One unit increased platelet will lower the risk of dying by 0.2% for the Cox model and 0.3% for the logistic model. The study conducted both in animals and humans reported a similar finding indicating that melioidosis patients with low platelet increased the risk of dying by 7.90 than melioidosis patients with normal platelet [57]. In another recent study based on 1999 to 2017 data, the result reported that there was a significant association between the lower platelet count during admission and mortality (P<0.001) [55].

Albumin was also a significant predictor of mortality in this study. The increased one g/L albumin lowered the odds of getting mortality from melioidosis by 3.6% (logistic model) and 0.1% (Cox Model). In the AFT model, those with one g/L increased albumin will develop faster the progression of survival by 9.6%. A prospective study in India aimed to identify the associated factors of mortality using the Cox analysis [58]. The study reported that a total of 83.8% of melioidosis patients had hypoalbuminemia. After applying the multivariable analysis using the Cox model, the final finding did not show any significant predictors towards mortality from melioidosis [58]. A study in Sarawak reported that serum albumin was also found as the predictor of mortality from melioidosis (P=0.031, OR= 0.73; 95% CI: 0.54, 0.97) [59].

Chronic lung disease was one of the comorbidity risk factors of mortality in this study. The current study found that those with chronic lung disease reduced the disease progression by 99.0% compared to those without chronic lung disease. Similarly, a similar finding reported that using multivariable logistic analysis, the odds of patients with chronic lung disease dying were four times compared to patients without chronic lung disease (95% CI: 1.84, 8.93) [60]. Based on Currie et al. 2010, patients with chronic lung disease had a 50% higher risk of dying from melioidosis than patients without chronic lung disease (95% CI: 1.1, 2.4) [51].

The variable pneumonia was found to be a significant determinant of mortality among melioidosis patients in this study. It was found that pneumonia slower the disease progression by 58.6%. The study in Southern Thailand supported the finding reported the odds ratio of dying from melioidosis among those with pneumonia was 12.25 compared to those without pneumonia (95% CI: 3.08, 48.73) [61]. It was reported the high number of death among in-hospital patients who had pneumonia (34%) versus those

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without pneumonia (18%) (P=0.007) [62]. The finding was also supported by several studies [50], [53].

The variable received the antibiotics was one of the most important risk factors of mortality from melioidosis. In this study, melioidosis patients who did not receive the antibiotics increased the odds of dying by 3.67 compared to those who received the antibiotics. A 10-year retrospective study in Thailand reported that inappropriate antibiotic administration during admission was significantly associated with a higher mortality rate in melioidosis patients with an OR of 37.67 (95% CI: 7.29, 238.94) [61]. Based on the multiple logistic analysis, a study that was conducted in Thailand demonstrated that melioidosis patients with appropriate antibiotics reduced the risk of mortality by 69% (95% CI: 0.12, 0.82) [63].

Based on the type of melioidosis distribution, bacteremic melioidosis showed a significant determinant of mortality from melioidosis in all three models. Hantrakun et al. 2019 reported the increased odds of dying from melioidosis in bacteremic patients (OR: 5.66, 95% CI: 4.93, 6.51, P<0.001). A Singapore study reported that bacteremic patients reduced the risk of surviving melioidosis by 98.0% (OR: 0.02, 95% CI: 0.00, 0.25) [64]. Many other studies are also in line with the current study's findings [61], [65].

Table 1. Studies on prognostic factors of mortality in melioidosis patients in Malaysia

Authors (year)	Study population, setting and period	Significant prognostic factors	Statistical analysis
Hassan *et al.* (2010)	Hospital Sultanah Bahiyah. n=145 melioidosis confirmed cases. January 2005.	Diabetes.	Poisson regressions.
Roslani *et al.* (2014)	A teaching hospital in Kuala Lumpur, Malaysia. n=85 patients August of 1988 – June of 2010	The regression model showed two independent predictors of severity, lower lymphocyte counts and presence of positive blood cultures.	Logistic regression analysis.
Zueter *et al.* (2016)	Hospital Universiti Sains Malaysia, Kubang Kerian, n=158 confirmed cases of melioidosis . 2001 – 2015.	The presence of at least one co-morbid factor, the happening of septic shock, and age > 40 years.	Logistic regression analysis.
Hassan *et al.* (2018)	Hospital Sultanah Bahiyah (HSB), Alor Setar n=254 confirmed melioidosis cases. 2005 – 2011.	Gender (males), race, occupation (farming), and co-occurring chronic diseases, particularly diabetes.	Conditional logistic regression analysis
Toh *et al.* (2020)	Kapit Hospital, Sarawak. n=73 melioidosis patients. 3 years period.	Serum bicarbonate and serum albumin.	Multiple logistic regression.

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Mardhiah *et al.* (2021) [66]	Hospital Universiti Sains Malaysia n=453 melioidosis patients 2014 – 2019	High white blood cell, low platelet, low level of urea, bacteremic	Multiple logistic regression.
Mardhiah *et al.* (2021)[26]	Hospital Universiti Sains Malaysia n=453 melioidosis patients 2014 – 2019	Diabetes mellitus, type of melioidosis, platelet count, white blood cell count, and urea value	Cox proportional hazards regression
Toh *et al.* (2021)	Kapit Hospital, Sarawak. n=73 melioidosis patients. 3 years period.	Serum bicarbonate and serum albumin.	Multiple logistic regression.

3. Conclusions

The results from the study seven studies were selected based on the endemic areas of melioidosis in Malaysia. The study findings were reviewed to compare the statistical method in analyzing the melioidosis data and create awareness about the disease to the healthcare provider and clinicians. Based on the current study, several recommendations are suggested for future studies. Firstly, it is suggested that the cost-effectiveness of melioidosis treatment will be performed with proper management of the variables collected to identify the economic burden associated with melioidosis patients. Since the research on cost analysis is still limited in Malaysia, the data will contribute a lot of information to developing research in Malaysia.

Other than that, a prospective study would be better conducted for future studies to determine the real timing of melioidosis diagnosis. The date of admission was the only data available from the medical record that can predict the time of diagnosis for the study. Since lack of clinical suspicion and delay in diagnosis or treatment were so common in melioidosis, these critical uncertainties will provide a good result in assessing the prognostic factors of mortality in melioidosis.

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