

Review

Not peer-reviewed version

A Review of the Study Designs and Statistical Methods Used in the Determination of Predictors of Melioidosis Mortality in Malaysia: 2010–2021

[Kamaruddin Mardhiah](#)*

Posted Date: 21 December 2023

doi: 10.20944/preprints202312.1592.v1

Keywords: Study design; statistical methods; melioidosis; infectious disease; mortality; risk factors; prognostic factors; predictors



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Review

A Review of the Study Designs and Statistical Methods Used in the Determination of Predictors of Melioidosis Mortality in Malaysia: 2010–2021

Kamaruddin Mardhiah

Faculty of Entrepreneurship and Business, Universiti Malaysia Kelantan, Kelantan, Malaysia; mardhiah.k@umk.edu.my

Abstract: Background: 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. **Objective:** To give an overview of the study designs, statistical methods and comparison of research in identifying the predictors of melioidosis mortality in Malaysia between January 2010 to December 2021. This review articles were divided into two sections; Section 1: Review of literature and Section 2: Findings on predictors of melioidosis mortality in Malaysia. **Data sources:** Pubmed/Medline. **Study Eligibility Criteria:** Original English-language articles were abstracted. The articles that identified the predictors of melioidosis from mortality in Malaysia only included. Letters to the editor, editorials, reviews, systematic reviews, meta-analysis, case reports and any other ineligible articles were excluded. **Results:** A total of 7 studies were identified related to predictors of melioidosis mortality in Malaysia. From the selected articles, all of the data were retrospectively collected. Six out of 7 articles (85.7%) used the logistic regression in identifying the predictors of melioidosis mortality. Only 1 (14.3%) used advanced survival analysis methods of Cox regression analysis. **Conclusion:** Logistic regression methods remain the most common methods of analysis in publications on predictors of melioidosis mortality in Malaysia while retrospective research designs are favoured. There is a limitation of research in predictors of melioidosis mortality and the use of advanced statistical techniques reported using the melioidosis data in Malaysia. 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 prognostic factors of this disease.

Keywords: Study design; statistical methods; melioidosis; infectious disease; mortality; risk factors; prognostic factors; predictors

WHAT WE ALREADY KNOW

The global burden of melioidosis was proven worldwide by increasing the number of deaths from this disease. Melioidosis is considered a notifiable disease in Malaysia, with a low clinical suspicion among the physicians that lead to misdiagnosis and mismanagement of melioidosis patients. Malaysia is also considered an endemic hot spot for melioidosis, with a high number of mortality cases reported per year. Several studies in Malaysia had reported on the factors associating of mortality from melioidosis.

WHAT THIS ARTICLE ADDS

There are currently limited published studies about melioidosis in Malaysia, both in academics and laboratories. Besides, no published study in Malaysia compares the findings on the factors contributing to the mortality from melioidosis in Malaysia. This review article provides a comparison of the results from eight articles in Malaysia that analyzed the factors associated with mortality in Malaysia.

SECTION 1: REVIEW OF LITERATURE

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 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].

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–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].

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 Puthuchery (2009), to be more precise, melioidosis can be classified into septicemic and non-septicemic [10].

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].

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, 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*.

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

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].

Incidence of 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].

SECTION 2: FINDINGS ON MORTALITY OF MELIOIDOSIS IN MALAYSIA

Methods

Search strategies and selection criteria

In this bibliometric analysis, all original English language articles indexed in Pubmed/Medline were searched using Boolean operators, brainstorming and expanding the keywords, and refining the search results. The Boolean “AND” was used to broaden the search. The keywords used for the predictors mortality of melioidosis were “mortality AND melioidosis,” “prognostic factors AND

mortality AND melioidosis,” “risk factors AND mortality AND melioidosis,” and “predictors AND mortality AND melioidosis.” Other than that, the terms that were used includes, “Predictors of melioidosis Mortality in Malaysia”, “Determinants of melioidosis mortality in Malaysia”, “Prognostic factors of melioidosis mortality in Malaysia” and “Factors associated with melioidosis mortality in Malaysia”. The search covered the period between January 2010 and December 2021.

Original articles on melioidosis within the specified period in Malaysia were eligible for inclusion. Letters to the editor, editorials, reviews, systematic reviews, meta-analysis and case reports were excluded. From the literature search, three hundred and three articles related to mortality from melioidosis in Malaysia were found. After the screening, only seven articles with research based on the predictors of mortality in Malaysia between 2010 – 2021 were selected and reviewed. Each article was reviewed to determine the study design, nature of statistical methods used and comparison of the findings between the articles.

The data collection was made based on the checklist of the items of interest. The findings from the selected articles were recorded and classified according to the statistical technique used and findings of the predictors of mortality from melioidosis.

Results

The total number of studies reporting on predictors of melioidosis mortality that met the inclusion of the study criteria between January 2010 to December 2021 was 10 articles. All the identified articles were reported using the statistical methods on identifying the predictors of melioidosis mortality in Malaysia. Journal of Acquired Immune Infection (JAIDS) (n = 34, 18%) and AIDS (n = 24, 13%) published more articles on HIV mortality. JAIDS and AIDS published 19/34 (56%) and 14/24 (58%) of these articles in the era 2002–2006. All the articles used a retrospective study design. The lowest sample size was 73 and the highest was 453. Table 1 presents the study design and sample size distribution of the included articles.

Table 1. Types of locations, study designs and sample sizes.

Authors	Locations	Study design	Sample size
Hassan <i>et al.</i> (2010)	Hospital Sultanah Bahiyah (HSB), Alor Setar.		145
Roslani <i>et al.</i> (2014)	Teaching hospital in Kuala Lumpur, Malaysia.	Retrospective	132
Zueter <i>et al.</i> (2016)	Hospital Universiti Sains Malaysia, Kubang Kerian.	Retrospective	158
Hassan <i>et al.</i> (2018)	Hospital Sultanah Bahiyah (HSB), Alor Setar.	Retrospective	254
Mardhiah <i>et al.</i> (2021) [66] [26]	Hospital Sultanah Bahiyah (HSB), Alor Setar.	Retrospective	453
Toh <i>et al.</i> (2021)	Kapit Hospital, Sarawak.	Retrospective	73

The number of studies reporting descriptive statistics for the two periods was similar. Table 3 presents the distribution of commonly reported statistical methods. The number of articles reporting

use of t-tests, contingency table analysis, correlation and epidemiological statistics was similar. Few studies in both periods reported using one-way analysis of variance technique (ANOVA). The number of modeling approaches such as logistic, conditional logistic, generalized estimating equations and Poisson regression was significantly higher in the later period compared to the earlier (n = 31, 32% vs. n = 13, 14% p = 0.005). A total of 122 (65%) articles reported using the Kaplan-Meier methods and it was commonly used in the first period compared to the second (p = 0.002). Use of the Cox proportional hazards regression modeling was reported by 131 (69%) articles and the number was similar between the two eras (p = 0.12). The number reporting use of time dependent Cox regression was higher in the first period (n = 21, 23% vs. n = 11, 11%; p = 0.03). Overall Cox regression with frailty was scarcely used (n = 7, 4%) in which 6 (3%) articles were in the later period. There were 22 (12%), 96 (51%) and 71 (38%) articles reporting use of 2 to 3, 4 to 5 and more than 5 statistical methods respectively. There were no significant differences in the number of methods used between the two eras. Similarly there were no significant differences between the two eras in the number of

Table 2. Summary of statistical methods used and findings for predictors of melioidosis mortality.

Authors	Statistical methods	Significant predictors of melioidosis mortality
Hassan <i>et al.</i> (2010)		
Roslani <i>et al.</i> (2014)		
Zueter <i>et al.</i> (2016)	Logistic regression	<ul style="list-style-type: none"> • Presence of at least one co-morbid • Septic shock • Age > 40 years
Hassan <i>et al.</i> (2018)		<ul style="list-style-type: none"> • Older age • Having diabetes mellitus • Having an unknown-risk for occupation or having an unknown smoking status • Having underlying infection of diabetes mellitus or chronic renal failure.
Mardhiah <i>et al.</i> (2021) [66] [26]		
Toh <i>et al.</i> (2021)		

Year	Authors	Study population, setting and period	Significant prognostic factors	Statistical analysis
2018	Hassan <i>et al.</i>	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

2020	Toh <i>et al.</i>	Kapit Hospital, Sarawak. n=73 melioidosis patients. 3 years period.	Serum bicarbonate and serum albumin.	Multiple logistic regression.
2021	Mardhiah <i>et al.</i> [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.
2021	Mardhiah <i>et al.</i> [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
2021	Toh <i>et al.</i>	Kapit Hospital, Sarawak. n=73 melioidosis patients. 3 years period.	Serum bicarbonate and serum albumin.	Multiple logistic regression.

Comparison of predictors of melioidosis mortality between the published articles

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-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 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.

Year	Authors	Study population, setting and period	Significant prognostic factors	Statistical analysis
------	---------	--------------------------------------	--------------------------------	----------------------

2010	Hassan <i>et al.</i>	Hospital Sultanah Bahiyah. n=145 melioidosis confirmed cases. January 2005.	Diabetes.	Poisson regressions.
2014	Roslani <i>et al.</i>	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.
2016	Zueter <i>et al.</i>	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.
2018	Hassan <i>et al.</i>	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
2020	Toh <i>et al.</i>	Kapit Hospital, Sarawak. n=73 melioidosis patients. 3 years period.	Serum bicarbonate and serum albumin.	Multiple logistic regression.

2021	Mardhiah <i>et al.</i> [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.
2021	Mardhiah <i>et al.</i> [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
2021	Toh <i>et al.</i>	Kapit Hospital, Sarawak. n=73 melioidosis patients. 3 years period.	Serum bicarbonate and serum albumin.	Multiple logistic regression.

CONCLUSION

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.

References

1. N. S. K. Ramli, C. Eng Guan, S. Nathan, and J. Vadivelu, "The Effect of Environmental Conditions on Biofilm Formation of Burkholderia pseudomallei Clinical Isolates," *PLoS One*, vol. 7, no. 9, 2012, doi: 10.1371/journal.pone.0044104.
2. S. Nathan *et al.*, "Melioidosis in Malaysia: Incidence, clinical challenges, and advances in understanding pathogenesis," *Trop. Med. Infect. Dis.*, vol. 3, no. 1, 2018, doi: 10.3390/tropicalmed3010025.
3. D. Limmathurotsakul and S. J. Peacock, "Melioidosis: A clinical overview," *Br. Med. Bull.*, vol. 99, no. 1, pp. 125–139, 2011, doi: 10.1093/bmb/ldr007.
4. A. L. Walsh *et al.*, "Prognostic significance of quantitative bacteremia in septicemic melioidosis," *Clin. Infect. Dis.*, vol. 21, no. 6, pp. 1498–1500, 1995, doi: 10.1093/clinids/21.6.1498.

5. M. H. Silbermann, I. C. Gyssens, H. P. Endtz, E. J. Kuijper, and J. T. M. Van Der Meer, "Two patients with recurrent melioidosis after prolonged antibiotic therapy," *Scand. J. Infect. Dis.*, vol. 29, no. 2, pp. 199–201, 1997, doi: 10.3109/00365549709035886.
6. C. Tiangpitayakorn, S. Songsivilai, N. Piyasangthong, and T. Dharakul, "Speed of detection of *Burkholderia pseudomallei* in blood cultures and its correlation with the clinical outcome," *Am. J. Trop. Med. Hyg.*, vol. 57, no. 1, pp. 96–99, 1997, doi: 10.4269/ajtmh.1997.57.96.
7. A. B. Malczewski, K. M. Oman, R. E. Norton, and N. Ketheesan, "Clinical presentation of melioidosis in Queensland, Australia," *Trans. R. Soc. Trop. Med. Hyg.*, vol. 99, no. 11, pp. 856–860, 2005, doi: 10.1016/j.trstmh.2005.06.015.
8. V. K. Jain, D. Jain, H. Kataria, and A. Shukla, "PRACTITIONERS' SECTION MELIOIDOSIS : A REVIEW OF ORTHOPEDIC MANIFESTATIONS , CLINICAL FEATURES , DIAGNOSIS AND MANAGEMENT Th is a PD si F te is ho a st va (w ed ilab w by le w . M f m e or ed d fr kn kno ee ow w do . c Pu wn om b lo). lica ad tio fr ns," 1950.
9. B. J. Currie *et al.*, "Melioidosis epidemiology and risk factors from a prospective whole-population study in northern Australia," *Trop. Med. Int. Heal.*, vol. 9, no. 11, pp. 1167–1174, 2004, doi: 10.1111/j.1365-3156.2004.01328.x.
10. S. D. Puthuchery, "Melioidosis in Malaysia," *Med. J. Malaysia*, vol. 64, no. 4, pp. 266–274, 2009, doi: 10.4269/ajtmh.1969.18.703.
11. W. J. Wiersinga *et al.*, "HHS Public Access," 2019, doi: 10.1038/nrdp.2017.107.Melioidosis.
12. D. Limmathurotsakul *et al.*, "Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis," *Nat. Microbiol.*, vol. 1, no. 1, pp. 1–13, 2016, doi: 10.1038/nmicrobiol.2015.8.
13. B. J. Currie, "Melioidosis: Evolving concepts in epidemiology, pathogenesis, and treatment," *Semin. Respir. Crit. Care Med.*, vol. 36, no. 1, pp. 111–125, 2015, doi: 10.1055/s-0034-1398389.
14. E. Birnie, H. S. Virk, J. Savelkoel, R. Spijker, P. D. A. B. Dance, and D. Limmathurotsakul, "Europe PMC Funders Group Global burden of melioidosis , 2015 : a systematic review and data synthesis," vol. 19, no. 8, pp. 892–902, 2020, doi: 10.1016/S1473-3099(19)30157-4.Global.
15. W. J. Wiersinga, B. J. Currie, and S. J. Peacock, "Medical progress: Melioidosis," *N. Engl. J. Med.*, vol. 367, no. 11, pp. 1035–1044, 2012, doi: 10.1056/NEJMra1204699.
16. S. W. Kim, G. Y. Kwon, B. Kim, D. Kwon, J. Shin, and G. R. Bae, "Imported Melioidosis in South Korea: A Case Series with a Literature Review," *Osong Public Heal. Res. Perspect.*, vol. 6, no. 6, pp. 363–368, 2015, doi: 10.1016/j.phrp.2015.10.014.
17. R. Perumal Samy, B. G. Stiles, G. Sethi, and L. H. K. Lim, "Melioidosis: Clinical impact and public health threat in the tropics," *PLoS Negl. Trop. Dis.*, vol. 11, no. 5, pp. 1–28, 2017, doi: 10.1371/journal.pntd.0004738.
18. C. Mcleod *et al.*, "Clinical presentation and medical management of melioidosis in children: A 24-Year Prospective study in the Northern Territory of Australia and review of the literature," *Clin. Infect. Dis.*, vol. 60, no. 1, pp. 21–26, 2015, doi: 10.1093/cid/ciu733.
19. P. S. Chen *et al.*, "Airborne transmission of melioidosis to humans from environmental aerosols contaminated with *B. pseudomallei*," *PLoS Negl. Trop. Dis.*, vol. 9, no. 6, pp. 1–16, 2015, doi: 10.1371/journal.pntd.0003834.
20. A. C. Cheng, S. P. Jacups, D. Gal, M. Mayo, and B. J. Currie, "Extreme weather events and environmental contamination are associated with case-clusters of melioidosis in the Northern Territory of Australia," *Int. J. Epidemiol.*, vol. 35, no. 2, pp. 323–329, 2006, doi: 10.1093/ije/dyi271.
21. J. Davie and C. W. Wells, "Equine melioidosis in Malaya," *Br. Vet. J.*, vol. 108, no. 5, pp. 161–167, 1952, doi: 10.1016/s0007-1935(17)51601-2.
22. S. H. How, K. H. Ng, A. R. Jamalludin, A. Shah, and Y. Rathor, "Melioidosis in Pahang, Malaysia," *Med. J. Malaysia*, vol. 60, no. 5, pp. 606–613, 2005.
23. M. Koshy *et al.*, "Clinical manifestations, antimicrobial drug susceptibility patterns, and outcomes in melioidosis cases, India," *Emerg. Infect. Dis.*, vol. 25, no. 2, pp. 316–320, 2019, doi: 10.3201/eid2502.170745.
24. A. Mohan *et al.*, "Pediatric melioidosis in Sarawak, Malaysia: Epidemiological, clinical and microbiological characteristics," *PLoS Negl. Trop. Dis.*, vol. 11, no. 6, pp. 1–11, 2017, doi: 10.1371/journal.pntd.0005650.
25. M. R. A. Hassan *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.*, vol. 10, no. 1, p. 302, 2010, doi: 10.1186/1471-2334-10-302.
26. K. Mardhiah, N. Wan-arfah, N. N. Naing, M. Radzi, A. Hassan, and H. Chan, "The Cox model of predicting mortality among melioidosis patients in Northern Malaysia," vol. 25, no. November 2020, 2021.
27. A. R. Zueter, C. Y. Yean, M. Abumarzouq, Z. A. Rahman, Z. Z. Deris, and A. Harun, "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.*, vol. 16, no. 1, pp. 1–11, 2016, doi: 10.1186/s12879-016-1583-2.

28. A. M. Zueter, M. Abumarzouq, M. I. Yusof, W. F. Wan Ismail, and A. Harun, "Osteoarticular and soft-tissue melioidosis in Malaysia: Clinical characteristics and molecular typing of the causative agent," *J. Infect. Dev. Ctries.*, vol. 11, no. 1, pp. 28–33, 2017, doi: 10.3855/jidc.7612.
29. Center for Food Security and Public Health, "The Organism," *New Scholasticism*, vol. 15, no. 3, pp. 286–289, 2011.
30. A. R. Hoffmaster *et al.*, "Melioidosis diagnostic workshop, 20131," *Emerg. Infect. Dis.*, vol. 21, no. 2, pp. 1–9, 2015, doi: 10.3201/eid2102.141045.
31. K. L. Woods *et al.*, "Evaluation of a rapid diagnostic test for detection of burkholderia pseudomallei in the Lao people's democratic republic," *J. Clin. Microbiol.*, vol. 56, no. 7, 2018, doi: 10.1128/JCM.02002-17.
32. M. R. Abu Hassan *et al.*, "Socio-epidemiological and land cover risk factors for melioidosis in Kedah, Northern Malaysia," *PLoS Negl. Trop. Dis.*, vol. 13, no. 3, 2018, doi: 10.1371/journal.pntd.0007243.
33. R. M. Aliyu, N. Mohamed Mustapha, Z. Zakaria, and S. K. Bejo, "Molecular detection, identification and differentiation of Burkholderia pseudomallei," *Pertanika J. Sch. Res. Rev.*, vol. 2, pp. 69–79, 2016.
34. Z. Z. Win *et al.*, "Use of rapid enzyme-linked immunosorbent assays for serological screening of melioidosis in myanmar," *Am. J. Trop. Med. Hyg.*, vol. 98, no. 5, pp. 1300–1302, 2018, doi: 10.4269/ajtmh.17-0791.
35. K. E. Vandana, "Septicaemic melioidosis: best approach to diagnosis," *Sri Lankan J. Infect. Dis.*, vol. 7, no. 0, p. 13, 2017, doi: 10.4038/sljid.v7i0.8180.
36. D. Limmathurotsakul *et al.*, "Increasing incidence of human melioidosis in northeast Thailand," *Am. J. Trop. Med. Hyg.*, vol. 82, no. 6, pp. 1113–1117, 2010, doi: 10.4269/ajtmh.2010.10-0038.
37. C. Mukhopadhyay, T. Shaw, G. M. Varghese, and D. A. B. Dance, "Melioidosis in South Asia (India, Nepal, Pakistan, Bhutan and Afghanistan)," *Trop. Med. Infect. Dis.*, vol. 3, no. 2, 2018, doi: 10.3390/tropicalmed3020051.
38. PMG Secretariat, "Guidelines For Clinical and Public Health Management of Melioidosis in Pahang," Pahang, malaysia.
39. M. Ip, L. G. Osterberg, P. Y. Chau, and T. A. Raffin, "Pulmonary melioidosis," *Chest*, vol. 108, no. 5, pp. 1420–1424, 1995, doi: 10.1378/chest.108.5.1420.
40. W. Chaowagul *et al.*, "Open-label randomized trial of oral trimethoprim-sulfamethoxazole, doxycycline, and chloramphenicol compared with trimethoprim-sulfamethoxazole and doxycycline for maintenance therapy of melioidosis," *Antimicrob. Agents Chemother.*, vol. 49, no. 10, pp. 4020–4025, 2005, doi: 10.1128/AAC.49.10.4020-4025.2005.
41. W. Chaowagul, A. J. H. Simpson, Y. Suputtamongkol, and N. J. White, "Empirical cephalosporin treatment of melioidosis," *Clin. Infect. Dis.*, vol. 28, no. 6, p. 1328, 1999, doi: 10.1086/517787.
42. A. C. Cheng, D. P. Stephens, N. M. Anstey, and B. J. Currie, "Adjunctive Granulocyte Colony-Stimulating Factor for Treatment of Septic Shock Due to Melioidosis," *Clin. Infect. Dis.*, vol. 38, no. 1, pp. 32–37, 2004, doi: 10.1086/380456.
43. V. Hantrakun *et al.*, "Cost-effectiveness analysis of parenteral antimicrobials for acute melioidosis in Thailand," *Trans. R. Soc. Trop. Med. Hyg.*, vol. 109, no. 6, pp. 416–418, 2015, doi: 10.1093/trstmh/trv002.
44. D. Dance, "Treatment and prophylaxis of melioidosis," *Int. J. Antimicrob. Agents*, vol. 43, no. 4, pp. 310–318, 2014, doi: 10.1016/j.ijantimicag.2014.01.005.
45. S. Bhengsri *et al.*, "Economic burden of bacteremic melioidosis in eastern and northeastern, Thailand," *Am. J. Trop. Med. Hyg.*, vol. 89, no. 2, pp. 369–373, 2013, doi: 10.4269/ajtmh.13-0148.
46. N. Luangasanatip *et al.*, "The global impact and cost-effectiveness of a melioidosis vaccine," *BMC Med.*, vol. 17, no. 1, pp. 1–11, 2019, doi: 10.1186/s12916-019-1358-x.
47. K. Mardhiah, N. Wan-Arfah, N. N. Naing, M. R. Abu Hassan, H. K. Chan, and H. Hasan, "The Trend of Direct Medical Cost of Melioidosis Patients in Kedah : A Retrospective Study from 2014 to 2017," pp. 155–162, 2021.
48. P. V. Kingsley, M. Leader, N. S. Nagodawithana, M. Tipre, and N. Sathiakumar, "Melioidosis in Malaysia: A Review of Case Reports," *PLoS Negl. Trop. Dis.*, vol. 10, no. 12, pp. 1–18, 2016, doi: 10.1371/journal.pntd.0005182.
49. L. Pagalavan, "Melioidosis: The Johor Bahru experience," *Med. J. Malaysia*, vol. 60, no. 5, pp. 599–605, 2005.
50. V. Hantrakun *et al.*, "Clinical epidemiology of 7126 melioidosis patients in Thailand and the implications for a national notifiable diseases surveillance system," *Open Forum Infect. Dis.*, vol. 6, no. 12, 2019, doi: 10.1093/ofid/ofz498.
51. B. J. Currie, L. Ward, and A. C. Cheng, "The epidemiology and clinical spectrum of melioidosis: 540 cases from the 20 year darwin prospective study," *PLoS Negl. Trop. Dis.*, vol. 4, no. 11, 2010, doi: 10.1371/journal.pntd.0000900.
52. S. Chinnakkulam Kandhasamy, T. Elamurugan, D. Naik, G. Rohith, and V. P. Nelamangala Ramakrishnaiah, "Systemic Melioidosis With Ruptured Splenic Abscess," *Cureus*, vol. 12, no. 5, 2020, doi: 10.7759/cureus.7956.

53. A. C. Cheng, S. P. Jacups, N. M. Anstey, and B. J. Curries, "A proposed scoring system for predicting mortality in melioidosis," *Trans. R. Soc. Trop. Med. Hyg.*, vol. 97, no. 5, pp. 577–581, 2003, doi: 10.1016/S0035-9203(03)80035-4.
54. A. K. Manimaran R, Anand S, "Melioidosis: a multiple disease imposter," *Int. J. Res. Med. Sci.*, vol. 6, no. 8, p. 2872, 2018, doi: 10.18203/2320-6012.ijrms20183287.
55. P. Kirby, S. Smith, L. Ward, J. Hanson, and B. J. Currie, "Clinical utility of platelet count as a prognostic marker for melioidosis," *Am. J. Trop. Med. Hyg.*, vol. 100, no. 5, pp. 1085–1087, 2019, doi: 10.4269/ajtmh.18-0698.
56. P. Domthong, S. Chaisuksant, and K. Sawanyawisuth, "What clinical factors are associated with mortality in septicemic melioidosis? A report from an endemic area," *J. Infect. Dev. Ctries.*, vol. 10, no. 4, pp. 404–409, 2016, doi: 10.3855/jidc.6455.
57. E. Birnie *et al.*, "Thrombocytopenia Impairs Host Defense Against *Burkholderia pseudomallei* (Melioidosis)," *J. Infect. Dis.*, vol. 219, no. 4, pp. 648–659, 2019, doi: 10.1093/infdis/jiy541.
58. A. Basheer, N. Iqbal, S. C. R. Kanungo, and R. Kandasamy, "Melioidosis: distinctive clinico-epidemiological characteristics in southern India," *Trop. Doct.*, pp. 5–8, 2020, doi: 10.1177/0049475520943698.
59. V. Toh, S. P. Tee, D. Ang, and C. Y. Chang, "Predicting the mortality of melioidosis in the heart of Borneo," *Int. J. Infect. Dis.*, p. 4633, 2020, doi: 10.1016/j.ijid.2020.09.585.
60. J. Hanson and S. Smith, "High rates of premature and potentially preventable death among patients surviving melioidosis in Tropical Australia," *Am. J. Trop. Med. Hyg.*, vol. 101, no. 2, pp. 328–331, 2019, doi: 10.4269/ajtmh.19-0375.
61. C. Churuangsuk, S. Chusri, T. Hortiwakul, B. Charernmak, and K. Silpapojakul, "Characteristics, clinical outcomes and factors influencing mortality of patients with melioidosis in southern Thailand: A 10-year retrospective study," *Asian Pac. J. Trop. Med.*, vol. 9, no. 3, pp. 256–260, 2016, doi: 10.1016/j.apjtm.2016.01.034.
62. A. Jatapai *et al.*, "Hospitalized bacteremic melioidosis in rural Thailand: 2009–2013," *Am. J. Trop. Med. Hyg.*, vol. 98, no. 6, pp. 1585–1591, 2018, doi: 10.4269/ajtmh.17-0402.
63. S. Ruangsupanth *et al.*, "Appropriate use of antibiotics and patient outcomes in melioidosis," *Malaysian J. Pharm. Sci.*, vol. 2, no. 1, pp. 9–20, 2004.
64. J. M. F. Chien, S. E. Saffari, A. L. Tan, and T. T. Tan, "Factors affecting clinical outcomes in the management of melioidosis in Singapore: a 16-year case series," *BMC Infect. Dis.*, vol. 18, no. 1, p. 482, 2018, doi: 10.1186/s12879-018-3393-1.
65. A. D. R. M. Roslani, S. T. Tay, S. D. Puthuchery, D. V. Rukumani, and I. C. Sam, "Short report: Predictors of severe disease in Melioidosis patients in Kuala Lumpur, Malaysia," *Am. J. Trop. Med. Hyg.*, vol. 91, no. 6, pp. 1176–1178, 2014, doi: 10.4269/ajtmh.14-0354.
66. K. Mardhiah, N. Wan-Arfah, N. N. Naing, M. R. A. Hassan, and H. K. Chan, "Predictors of in-hospital mortality by logistic regression analysis among melioidosis patients in Northern Malaysia: A retrospective study," *Asian Pac. J. Trop. Med.*, vol. 14, no. 8, pp. 356–363, 2021, doi: 10.4103/1995-7645.321612.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.