MODESTUM

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An overview of the study designs and statistical methods used in the determination of predictors of melioidosis mortality in Malaysia: 2010-2021

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ARTICLE INFO	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. **Objectives:** The objective of the study was 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. **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 eight studies were identified related to predictors of melioidosis mortality in Malaysia. From the selected articles, 87.5% were retrospectively collected. Five out of eight articles (62.5%) used the logistic regression in identifying the predictors of melioidosis mortality. Only one (12.5%) used advanced survival analysis methods of Cox regression analysis. Another 25.0% used Chi-square test. **Conclusions:** Logistic regression methods remain the most common methods of analysis in publications on predictors of melioidosis mortality in Malaysia while retrospective research designs are preferred. 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 prognosis factors of this disease. **Keywords:** overview, review, study design, statistical methods, melioidosis, infectious disease, mortality, risk factors, prognostic factors, predictors, statistical test

INTRODUCTION

The word melioidosis is a derivative of Greek words and was invented in 1921 by Stanton and Fletcher. The meaning of the word "melis" is "a distemper of asses," and "eidos" meaning is a resemblance. The words were derived because melioidosis was similar to glanders clinically and pathologically (Davie & Wells, 1952). Melioidosis was first discovered in Rangoon, Burma, in 1911 by Whitmore and Krishnaswami by a total of 38 fatal cases (Puthucheary, 2009). The first animal case (pig) reported in Africa around 1936 (Wiersinga et al., 2018).

Melioidosis is caused by a bacteria known as *Burkholderia pseudomallei* (Yabuuchi et al., 1992). The bacteria has been previously known as *Bacillus pseudomallei*, *Bacillus whitmorii* (or *Bacille de Whitmore*), *Malleomyces pseudomallei*, *Pseudomonas pseudomallei*. In 1992, it was officially named as *Burkholderia pseudomallei* (Yabuuchi et al., 1992). The environmental factor was highly associated with the increase of *B. pseudomallei* distribution in effected areas. The presence of bacteria was associated with the high rainfall and temperature, soil with anthrosol and acrisol condition, high salinity and high proportion of gravel, and level of soil pH (Limmathurotsakul et al., 2016).

The incidence of melioidosis has increased dramatically in recent decades. In Malaysia, the first cases were reported in Kuala Lumpur around 1913 (Davie & Wells, 1952). The spread of the disease occurred after the 2nd World War in Malaysia, Thailand, and Burma, with 10 cases reported in Malaysia (Puthucheary, 2009). 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

(Puthucheary, 2009). In 1994, the 1st 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.

Incidence may vary between states, and even within the same state, there may be various hotspots (Mohan et al., 2017). 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 (Abu Hassan et al., 2010).

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 (Birnie et al., 2020). The disease ordinarily occurs in people aged 40 to 60 and males (Wiersinga et al., 2018). Melioidosis mostly affects vulnerable persons who are directly in contact with polluted wet soil (Kim et al., 2015). The elderly with low immune systems, especially those suffering from diabetes mellitus and/or alcoholism, are at risk of developing infection (Samy et al., 2017).

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 (Mardhiah et al., 2021b). 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 (Kim et al., 2015; Limmathurotsakul et al., 2016), the ratio of males compared to females was higher. The majority of patients were Malay since the state is dominated by the Malay population (Abu Hassan et al., 2010; Mardhiah et al., 2021b; Zeuter et al., 2016).

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 (Samy et al., 2017). In 1932, the mortality rate reported was 98.0%, with 83 cases in South and Southeast Asia (Wiersinga et al., 2018).

Based on the published report from 1975 to 2015, 67 cases were reported in Malaysia, with 43.0% (29 cases) mortality (Kingsley et al., 2016). A study conducted in Hospital Universiti Sains Malaysia, Kubang Kerian, reported 33.0% mortality from 2001 to 2015 (Zeuter et al., 2016). Another study conducted in Alor Setar, Kedah, also reported that the mortality rate was 34.0% from 2005 to 2008 (Abu Hassan et al., 2010). How et al. (2005) reported the percentage of deaths in Kuantan, Pahang from 2000 to 2003 was 54.0% higher than in Kedah and Kelantan. Another study in Kuala Lumpur reported a higher number of deaths among bacteremia melioidosis cases, with 65.0% deaths from 1976 to 1991 (Kingsley et al., 2016).

In Johor Bharu, the mortality rate was 47.7% from 1999 to 2003, where eight out of the 21 patients (38.1%) and nine (42.9%) died within 24 hours of admission and died after 72 hours of admission, respectively (Pagalavan, 2005). Another mixed prospective and retrospective study that was conducted at three major hospitals in Sarawak reported a percentage of 43.0% of children died from melioidosis (Mohan et al., 2017).

The efforts of this review was to fill the gap in melioidosis research in Malaysia. This study is important as so far there are lack of studies that provide a research on predictor of mortality among melioidosis patients in Malaysia. This article review is vital because Malaysia is one of the endemic hot spot for melioidosis with a high number of mortality cases reported per year (Nathan et al., 2018). To construct a relevant review, the current article was guided by the main research question–what is the predictors of mortality among the melioidosis patients in Malaysia? The main focus of the study was on the predictors of melioidosis mortality in order to create awareness of the disease and the importance of prevention and managing melioidosis to avoid mortality.

METHODS

Search Strategies & 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. 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 study locations, sample size, study design, statistical technique used and findings of the predictors of mortality from melioidosis.

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

Authors	Locations	Study design	Sample size
Abu Hassan et al. (2010)	Hospital Sultanah Bahiyah, Alor Setar	Retrospective	145
Zueter et al. (2016)	Hospital Universiti Sains Malaysia, Kubang Kerian	Retrospective	158
Hassan et al. (2019)	Hospital Sultanah Bahiyah, Alor Setar	Retrospective	254
Tang et al. (2019)	Hospital Teluk Intan	Retrospective	46
Ali et al. (2020)	All health institutions across Kedah & Perlis states	Cross-sectional	512
Mardhiah et al. (2021a, 2021b)	Hospital Sultanah Bahiyah, Alor Setar	Retrospective	453
Toh et al. (2020)	Kapit Hospital, Sarawak	Retrospective	73

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

Authors	Statistical methods	Significant predictors of melioidosis mortality
Abu Hassan et al. (2010)	Poisson regression	• Having diabetes mellitus
Zueter et al. (2016)	Logistic regression	• Presence of at least one co-morbid • Septic shock • Age >40 years
Hassan et al. (2019)	Conditional logistic regression	• 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
Tang et al. (2019)	Chi-square	• All predictors not significant
Ali et al. (2020)	Chi-square	• Age group • Occupation • Pneumonia • Soft tissue abscess • Splenic abscess • Liver abscess • Septic shock • Initial treatment • Albumin • White blood cell
Mardhiah et al. (2021a)	Logistic regression	• High white blood cell • Low platelet • High level of urea • Bacteremia
Mardhiah et al. (2021b)	Cox proportional hazards regression	• High white blood cell • Low platelet • Low level of urea • Bacteremia • Diabetes mellitus
Toh et al. (2020)	Logistic regression	• Low serum bicarbonate • Low serum albumin

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 seven articles. All the identified articles were reported using the statistical methods on identifying the predictors of melioidosis mortality in Malaysia. Six articles used a retrospective study design and one article used cross-sectional study design. The lowest sample size was 73 and the highest was 512. Based on study location, the reported research focused on Northern Malaysia. One study each reported in Kelantan, Teluk Intan, and Kapit. **Table 1** presents the study design and sample size distribution of the included articles.

Table 2 presents the used of statistical methods and reported predictors of melioidosis mortality. From the review, Abu Hassan et al. (2010) used the Poisson regression while other authors used the traditional logistic regression in identifying the predictors of mortality from melioidosis. Only Mardhiah et al. (2021b) used the Cox proportional hazard regression to identify the predictors of mortality from melioidosis. Ali et al. (2020) used the basic statistics, which was chi-square to identify the factors associated with mortality from melioidosis. Other than that, basic statistics like t-test, ANOVA, and contingency table analysis used to compared the factors between those who alive and died in majority of the articles. According to year, the published articles were increase in year 2021. There was no published articled reported using the Kaplan-Meier method and limitation in using the advanced survival analysis.

The relation between older age and mortality from the melioidosis were showed statistically significant in two articles, Abu Hassan et al. (2010) and Zueter et al. (2016), urea was found to be a prognostic factor towards mortality from melioidosis in study conducted by Mardhiah et al. (2021a). The result demonstrating that increased one mmol/L of urea will increase the risk of dying from melioidosis. Several studies outside Malaysia showed a significant correlation between elevated urea and mortality among melioidosis patients (Cheng et al., 2003; Kirby et al., 2019; Rajendran et al., 2018).

Other than that, platelet count was also one of the prognostic factors of mortality from melioidosis in Mardhiah et al. (2021a). From the reported findings, it demonstrated that one unit increased platelet will lower the risk of dying by 0.2% for the Cox 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 (Birnie et l., 2019). 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) (Kirby et al., 2019).

A study by Toh et al. (2020) reported that serum albumin was also found as the predictor of mortality from melioidosis (p=0.031, odds ratio=0.73; 95% confidence interval: 0.54, 0.97). A prospective study in India aimed to identify the associated factors of mortality using the Cox analysis (Basheer et al., 2021). 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(Basheer et al., 2021). Based on the type of melioidosis distribution, bacteremia melioidosis showed a significant determinant of mortality from melioidosis in Mardhiah et al. (2021a). Many other studies are also in line with the study's findings (Chien et al., 2018; Churuangsuk et al., 2016; Hantrakun et al., 2019; Roslani et al., 2014).

DISCUSSION

This paper aimed at reviewing articles on predictors of mortality in melioidosis patients to investigate the application of statistical methods used and nature of study designs. The study wants to highlight the limitation of research of melioidosis mortality in Malaysia. Retrospective study designs remain the most common type of design used in studies of predictors of melioidosis mortality in Malaysia. It may be that retrospective study designs are used as a cost-effective way of saving on huge expenses required for running prospective studies as a way for stimulating academic research. However, a prospective study would be better conducted for future studies in predicting the determinants of melioidosis mortality as the real timing of melioidosis diagnosis can be accurately obtained. 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.

Most of the statistical method applied to obtain the following prognostic factors were logistic regression and retrospective was applied in most of articles in this study. In response towards this, most of the studies were not using the optimum statistical tests in the determination of the predictors of melioidosis mortality. The development of the regression analysis has developed to several extensions from the original model. It is important to select the best statistical analysis for the real dataset. To ensure that the statistical methods capture the data variability and all the sources from the data correctly, the data collection method, the assumptions of the analysis, and how the analysis was chosen to need to be considered (Greenland et al., 2016). Survival analysis methods produce enhanced estimates that are more instructive. In clinical research, the Cox regression analysis was widely used when involving the study with time to event outcome. AFT survival analysis was commonly used in industrial design and found to be new and unfamiliar in publishing clinical research papers (Kay & Kinnersley, 2002 ; Mardhiah et al., 2022). Both of these survival methods provide a better picture compared to logistic regression when using survival data. Additionally, it is practical to adjust for confounding variables by using optimal statistical methods when the study requires a multivariable analysis approach (Birnie et al., 2019).

CONCLUSIONS

This review has highlighted the statistical methods and study designs on research predicting the mortality form melioidosis in Malaysia. Within the Malaysian context, having diabetes, older age, presence of comorbidities, septic shock, abnormal blood function, and bacteremia melioidosis were the prognostic factors of mortality among the melioidosis patients. It also can be concluded that the recent advanced techniques were not implemented in predictors of mortality research in Malaysia. Based on the review, researchers more likely used the straight-forward and standard statistical software.

The proper management of the patient needs to be improved by providing more research on melioidosis to create awareness of the disease and the importance of prevention and managing melioidosis to avoid mortality. In order to provide more precise results regarding the disease, the advanced statistical analyses need to be applied in the study using the well-managed data and detailed planning of research methodology. Therefore, other than tackling the issue of limited studies on melioidosis in Malaysia and high mortality from melioidosis, the findings of the study provide the importance of reporting the high-quality statistical in scientific writing.

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