EMERGENCY PRESENTATIONS OF MELIOIDOSIS IN HOSPITAL USM: A TEN-YEAR REVIEW

BY

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LIST OF ABBREVIATIONS

ED	Emergency Department
HUSM	Hospital Universiti Sains Malaysia
BP	Blood Pressure
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
PR	Pulse Rate
RN	Registration Number
M	Male
F	Female
DOA	Date Of Admission
DOD	Date Of Discharge
SpO2	Oxygen saturation
WBC	White Blood Cell Count
AST	Aspartate Transaminase
ALT	Alanine Amino Transferase
ALP	Alkaline Phosphatase
PT	Prothrombin Time
INR	International Normalise Ratio
S/R	Sensitive/Resistence
IQR	Interquartile Range

ABSTRAK

CIRI-CIRI KLINIKAL YANG CEMAS BAGI PENYAKIT MELIOIDOSIS DI HOSPITAL USM:

KAJIAN SEPULUH TAHUN

Pengenalan

Melioidosis muncul sebagai satu masalah global, bagaimanapun, beberapa kajian telah diterangkan secara khusus tentang ciri-ciri klinikal dan status akhir kesihatan pesakit apabila dirawat di Jabatan Kecemasan (ED). Melioidosis ialah penyakit berjangkit tropika disebabkan oleh bakteria Gram-negatif *Burkholderia pseudomallei*. Diagnosis segera ialah satu cabaran besar kepada doktor di ED kerana kepelbagaian ciri-ciri klinikal penyakit melioidosis ini. Organ yang paling kerap terjejas oleh organisma ini adalah paru-paru. Walau bagaimanapun, adalah amat sukar untuk membezakan secara klinikal penyebab radang paru-paru oleh melioidosis dengan organisma lain.

Diandaikan bahawa hujan lebat berserta angin kencang membawa *B. pseudomallei* yang tertanam ke permukaan tanah; selepas itu, mereka lebih cenderung untuk disedut pada kepekatan yang tinggi dan menyebabkan kejutan septik yang teruk dan kematian awal. Kajian ini bertujuan untuk menentukan ciri-ciri klinikal dan profil makmal pesakit melioidosis yang datang ke ED, Hospital Universiti Sains Malaysia (HUSM), Kelantan.

Metodologi

Kajian ini merupakan kajian kohort retrospektif (penelitian rekod). Semua pesakit yang datang ke ED, HUSM dari Januari 2001 hingga Disember 2011 dengan sampel positif untuk melioidosis telah dimasukkan dalam kajian ini. Data dikumpul melalui pangkalan data berkomputer mikrobiologi hospital (WHO program-net) untuk calon individu dengan melioidosis. Data yang telah dimasukkan, dianalisis dengan menggunakan perisian SPSS versi 19.0 untuk menjana statistik deskriptif dan analitik.

Keputusan

Seramai 86 orang pesakit telah diteliti rekod mereka. Median pesakit berumur 51 tahun, 79.1% ialah lelaki dan 96.5% berbangsa Melayu. 91.9% daripada jumlah pesakit telah mengalami demam, diikuti dengan batuk (62.8%), dan sesak nafas (25.6%). Majoriti organ yang terlibat adalah paru-paru (65.1%), tisu lembut (19.8%), hati (18.6%), dan sendi (11.6%). Berdasarkan gejala tersebut, terdapat hubungan yang signifikan untuk batuk ($p = 0.02$), sesak nafas ($p = 0.001$) dan jangkitan tisu lembut ($p = 0.030$) dengan status akhir kesihatan pesakit.

Walaupun faktor-faktor risiko dijangkiti melioidosis yang paling kerap ialah diabetes (79.1%), diikuti dengan musim hujan (55.8%) dan terdedah kepada tanah (36%), tidak ada kaitan yang signifikan antara faktor-faktor risiko dan status akhir kesihatan pesakit. Semua penemuan fizikal didapati ada kaitan dengan status akhir kesihatan pesakit kecuali suhu badan ($p> 0.05$). Secara keseluruhan, semua profil makmal pesakit melioidosis adalah tinggi. Kaitan yang signifikan adalah pada urea ($p = 0.001$), kreatinin ($p = 0.001$), AST ($p = 0.002$) dan PT / INR ($p = 0.001$).

Dari segi penggunaan antibiotik secara empirikal, dan kelewatan masa sebelum memulakan terapi, tidak ada kaitan yang signifikan (p> 0.05) dengan status akhir kesihatan pesakit. Ketiadaan sesak nafas (SOB) (p = 0.017), tekanan darah sistolik (p = 0.049), tekanan darah diastolik (p = 0,018) dan PT / INR (p = 0.012) merupakan faktor penentu utama bagi pesakit untuk pulih daripada melioidosis. Oleh itu, model faktor penentu untuk pemulihan di kalangan pesakit melioidosis adalah:

Pemulihan (z) = 5.161 (Tiada SOB) -0.074 (SBP) + 0.186 (DBP) – 7.010 (PT / INR)

Formula Nagelkerke R Square menunjukkan bahawa kira-kira 76% daripada variasi dalam pembolehubah hasil (pemulihan) dijelaskan oleh model logistik ini dan ketepatan keseluruhan model ini untuk meramalkan subjek untuk kembali sembuh (dengan kebarangkalian yang diramalkan sebanyak 0.5 atau lebih besar) adalah 87.7% .

Kesimpulan

Ciri-ciri klinikal dan profil makmal boleh meramalkan status akhir kesihatan pesakit mengidap melioiosis. Tidak ada hubungan yang signifikan antara penggunaan antibiotik empirikal dan kelewatan masa sebelum memulakan terapi antimelioid dengan status akhir kesihatan pesakit yang mengidap melioidosis.

ABSTRACT

EMERGENCY PRESENTATIONS OF MELIOIDOSIS IN HOSPITAL USM: A TEN-YEAR REVIEW

Introduction

Melioidosis emerged as a global problem, however, few studies have specifically described the clinical characteristics and outcomes when patients with melioidosis are treated at an Emergency Department (ED). Melioidosis is a tropical infectious disease caused by Gram-negative bacteria *Burkholderia pseudomallei*. The prompt diagnosis of melioidosis is a great challenge to ED physicians because of the disease's diverse clinical presentations. The most common organ affected by this organism is lungs. However, it is very difficult to differentiate clinically the pneumonia causes by melioidosis with other organisms.

It is postulated that heavy rainfall with strong winds brings buried *B. pseudomallei* isolates to the soil surface; thereafter, they are more likely to be inhaled at high concentrations of the bacteria resulted in severe septic shock and early mortality. This study aimed to determine the clinical characteristics and laboratory profiles of patients with melioidosis that attended ED, Hospital Universiti Sains Malaysia (HUSM), Kelantan.

Methodology

This is a retrospective cohort study (record review). All patients presented to ED, HUSM from January 2001 till December 2011 with positive culture for melioidosis were included in the study. Data collected via hospital's computerized microbiology database (WHO-net program) for candidate individuals with melioidosis. Data entered and analyzed by using SPSS version 19.0 to generate descriptive and analytical statistics.

Results

A total of 86 patients were reviewed. Median age of the cases was 51 years old, males (79.1%) and Malays (96.5%). About 91.9% of the patients presented with fever, followed with cough (62.8%), and shortness of breath (25.6%). Majority of the organ involved were lung (65.1%), soft tissue (19.8%), liver (18.6%), and joints (11.6%). Base on symptoms, there were significant association for cough ($p=0.02$), shortness of breath ($p=0.001$) and abscess ($p=0.030$) with the outcomes.

Even though the most common risk factors were diabetes (79.1%), followed with rainy season (55.8%) and soil exposure (36%), there was no significant associations between risk factors and outcomes. All physical findings is significantly associated with the outcomes except for temperature ($p>0.05$). Overall, all laboratory profiles of melioidosis patients were deranged or prolonged. The only significant association were urea ($p=0.001$), creatinine ($p=0.001$), AST ($p=0.002$) and PT/INR ($p=0.001$).

In term of empirical antibiotic usage and time lag before initiation of therapy, there was no significance associations ($p>0.05$) with the outcomes. The absence of shortness of breath ($p=0.017$), systolic blood pressure ($p=0.049$), diastolic blood pressure ($p=0.018$) and PT/INR ($p=0.012$) were the main predictor for the patients to recover from melioidosis. Therefore, predictor model for recovery among melioidosis patient is:

$$\text{Recovery (z)} = 5.161\ (\text{No SOB}) - 0.074\ (\text{SBP}) + 0.186\ (\text{DBP}) - 7.010\ (\text{PT/INR})$$

The Nagelkerke R Square shows that about 76% of the variation in the outcome variable (recovery) is explained by this logistic model and the overall accuracy of this model to predict subjects to recover (with a predicted probability of 0.5 or greater) is 87.7%.

Conclusion

The clinical presentations and laboratory profiles can predict the outcomes of patient with melioidosis. There was no significant association between empirical usage of antibiotics and time lag before initiation of antimelioid therapy with the outcomes of melioidosis patients.

CHAPTER 1: INTRODUCTION

Melioidosis emerged as a global problem, however, few studies have specifically described the clinical characteristics and outcomes when patients with melioidosis are treated at ED (Wu *et al*., 2012). Melioidosis is a tropical infectious disease caused by Gram-negative bacteria *Burkholderia pseudomallei*. This soil-borne disease is endemic in Southeast Asia and Northern Australia. Melioidosis has a diverse spectrum of clinical presentations and can affect any organ. It is important to define the demographic profiles, clinical characteristics and outcomes of melioidosis because of the regional differences have been described in the prevalence of organ involvement (Malczewski *et al.*, 2005).

The prompt diagnosis of melioidosis is a great challenge to ED physicians because of the disease's diverse clinical presentations. A lack of clinical awareness and delays in obtaining bacteriologic identification that can result in inappropriate empiric antimicrobial selection and may place patients at a greater risk for mortality. A study by Deris *et al*(2010), indicated the early use of appropriate empirical antibiotics in ED may reduce the mortality due to bacteremic melioidosis. The most common organ affected by this organism is lungs. However, it is very difficult to differentiate clinically the pneumonia causes by melioidosis with other organisms.

Previous matched care-control study showed that the independent risk factors of pneumonic melioidosis were visiting the ED during the rainy season, poor control of glucose levels, and arriving in the ED in shock (Kung *et al*., 2011). Currie and Jacups also indicated that heavy rainfall in the 14 days before admission was an independent risk factor for pneumonia, septic shock, and death in patients with melioidosis (Currie *et al*., 2003). It is postulated that heavy rainfall with strong winds brings buried *B. pseudomallei* isolates to the soil surface; thereafter, they are more likely to be inhaled at high concentrations of the bacteria resulted in severe septic shock and early mortality.

Kelantan State, which is located in the northeastern part of Malaysia, has a heavy monsoon season from November to March every year. This state is located in what is known as the Malaysian rice bowl and has more than 60,000 hectares of paddy fields. Thousands of people are at risk of contracting *B. pseudomallei*, which is a great public health concern and an important cause of community acquired sepsis in the northeastern part of Malaysia (Deris *et al*., 2010). However, not many publications on meliodosis come from Malaysia. This study aimed to determine the clinical characteristics and laboratory profiles of patients with melioidosis that attended ED, HUSM, Kelantan.

CHAPTER 2. LITERATURE REVIEW

2.1 SOCIO-DEMOGRAPHICS OF THE CASES

Deris *et al.* (2010) reported that twenty patients (74.1%) were male. The mean age was 46.8 + 20.0 years with the youngest was 15 days old and the eldest was 80 years old. Based on study done by Ahmad *et al.* (2009*),* at Hospital Temerloh involving 33 patients in 2years, male is more prone to get melioidosis with ratio of 8:3 and age ranged from 40 to 65 years old. Relation with soil contact, there was no specific occupation correlated with the infection; however all three female patients were housewives. It was postulated that higher incidence of males with melioidosis may be due to their greater exposure to soil or contaminated water while engaging in agricultural activities.

Another study done in Pahang from January 2000 to June 2003 by How *et al.*(2005). That study found that 78.5% of the cases were male and Malay contributed 83% of the cases. Majority of the cases in Pahang aged 45 – 65 years old. In an another larger study by Puthucheary *et al*.(2009) in Malaysia, comprehensive review of 98 septicaemic and 43 nonsepticaemic cases were studied over a period of 35 years, there is a bimodal distribution of age in both groups of patients. Ranged from 17 days to 79 years of age, increase in the 10-30 years old group possibly reflects the greater environmental exposure during outdoor recreational activities.

Both males and female had the peak age-specific incidence occurred from 41 – 59 years. In every published case series on melioidosis, males have outnumbered females but the proportions varied considerably which likely reflects involvement in activities which lead to exposure to contaminated soil and water. In his study, the M:F ratio was found to be 3.2:1. No conclusion can be drawn regarding the correlation with the race group even the morbidity rate was highest amongst the Indians, lowest in Malays and intermediate in the Chinese. It is possible that the groups differed in their frequency of activities resulting in occupational and environmental exposure to soil and water.

In Brunei, a 6 years study by Pande *et al*.(2011) involving 14 out of 48 culture-positive patients (29%) were diagnosed with melioidosis of the extremities during the study period. Male population still predominantly involve as 13 male patients and one female patient, with a median age of 45 (range 14–55) years. A prospective observational study involving 31 patients by Ramamoorthi *et al*.(2013), the male to female ratio was 3:1. The median age was 48 years which fifty-two percent of patients were in the age group 41 to 60 years. By descriptive analysis, thirty-two of patients were agriculturists but no further analysis done to see the significance of it in correlation with melioidosis.

Study by Wu *et al*.(2012) involving total of 25 patients from emergency department in Taiwan, the mean age was 54 years which range between 35 to 87 years. Among them, 92% were male with ration of 23:2.

2.2 CLINICAL PRESENTATIONS OF MELIODOSIS CASES

A study by Deris *et al*.(2010) reported that the main clinical presentation was fever that occurred in 23 (85.2%) patients. Two patients presented with scrotal swelling, which later one developed Fournier's Gangrene. This presentation also reported by Puthucheary *et al*.(2009) The majority of patients presented with fever, the duration of which varied from l-2 d to 2-6 months, but in the latter the fever was not continuous. Pyrexia of unknown origin was diagnosed in two patients.

Similar result reported by Ramamoorthi et al.(2013), 87% (n = 27) of patients presented with fever, followed by cough in 35% (n = 11); breathlessness in 29% (n = 9) and jaundice in 20% (n = 6) of patients. The other presenting complaints were, skin and soft tissue swelling, joint pain-arthralgia, oliguria, abdominal pain, and a discharging axillary sinus. The pattern of fever varies, 16% of patients had fever of one-week duration; 55% of patients had fever duration of 7 to 30 days; 10% of patients had fever duration of 31 to 60 days.

2.3 ORGAN INVOLVEMENT IN MELIODOSIS

Deris *et al*.(2010) reported that lung involvement occurs in eighteen patients (66.7%) and three patients had liver abscess. Two patients presented with scrotal swelling, which later one of it complicated with Fournier's Gangrene. This also supported by Hassan *et al*.(2010), the study reported that pneumonia accounted for 42.06% of primary diagnoses followed by soft tissue abscess. Similar as studied by Wu *et al*.(2012), the most common infection site was the lungs (52%), followed by the genitourinary tract (28%) and the joints (16%). There was more than one site of infection in nine of the patients (36%).

A study in India by Ramamoorthi *et al*.(2013), most common organ involved was lung. Thirty-five percent (n = 11) of patients had pneumonia; 20% (n = 6) had pleural effusion; 3% (n = 1) had a mediastinal mass and 3% (n = 1) had a pyopneumothorax. The other organs involved as clinical presentation were multiple liver abscesses, splenic abscess, osteomyelitis, septic arthritis, cervical lymphadenopathy, submandibular lymph node abscess, parotid abscess, subcutaneous abscess in the back, and discharging axillary sinus. A 20 years prospective study by B.J. Currie *et al*.(2010) in Australia reported that the principal presentation was pneumonia in 278 (51%). Another presentations were genitourinary infection in 76 (14%), skin infection in 68 (13%), bacteremia without evident focus in 59 (11%), septic arthritis/osteomyelitis in 20 (4%) and neurological melioidosis in 14 (3%).

2.4 RISK FACTORS FOR MELIODOSIS

The most common risk factors were diabetes mellitus (79.1%) which some of them were newly diagnosed during that admission, followed with rainy season (55.8%), soil exposure (36.0%), chronic renal failure (10.5%) and malignancy (7.0%) (Deris *et al*., 2010). A total of 25 patients with melioidosis studied by Wu *et al*.(2012) in Taiwan, 84% were found to have at least one underlying condition, and diabetes mellitus (in 68% of patients) was the most common disease. Four patients (16%) had soil exposure, two were farmers and two were construction workers. Sixteen of the patients (64%) presented during the rainy season in Taiwan (between June and September).

Based on multivariable conditional logistic regression analysis, activities associated with a risk of melioidosis included working in a rice field, other activities associated with exposure to soil or water, an open wound, eating food contaminated with soil or dust, drinking untreated water, outdoor exposure to rain, water inhalation , current smoking and steroid intake. This organism *B. pseudomallei*, was detected in water source(s) consumed by 7% of cases and 3% of controls (Limmathurotsakul *et al.*, 2013)
The risk for developing and dying from melioidosis is high in patient with underlying diabetes, which occurring in 57% of all diagnosed cases. The other risk factors such as chronic renal failure, chronic lung disease, HIV, and other immunocompromised state were statistically not significant. But there were linear associations between cases and deaths with monthly rainfall. (Hassan *et al.*, 2010)

2.5 PHYSICAL AND LABORATORY FINDINGS IN MELIODOSIS

Study by Wu *et al*.(2012) in Taiwan show that the presence of band-form leukocytes (p=0.001), increased serum creatinine (p=0.037), and shock on arrival (p=0.005) were significantly more common among patients with early mortality. The other elevated blood parameters in patients with melioidosis were aspartate transaminase (AST) and blood glucose, but not contributing to early mortality.

Melioidosis was associated with activation of coagulation, suppression of anti-coagulation, and abnormalities of fibrinolysis. A study by Peacock *et al*.(2011), there was no haemostatic alterations were influenced by pre-existing diabetes. In the absence of infection, diabetes has a procoagulant effect. Even though diabetes itself is associated with multiple abnormalities of coagulation, anticoagulation and fibrinolysis, these changes are not detectable when superimposed on the background of larger abnormalities attributable to *B. pseudomallei* sepsis.

The blood parameters in patients with melioidosis may differ depending on severity of the disease during presentation to seek treatment. A study by Ramamoorthi *et al*.(2013) in India reported that 19 patients (61%) had total leucocyte count of more than 11,000 (cells/mm3).

2.6 MANAGEMENT OF MELIODOSIS

Treatment for melioidosis is usually divided into two phases. The first phase or acute phase, the aim is to prevent death from overwhelming sepsis. The parenteral drugs are given more than 10days. In the second phase or eradication phase, relapse prevention is done by completing with oral drugs for a total of 20weeks. Each treatment is tailored to individual patient's needs. Ceftazidime is the main drug used for treatment of melioidosis in acute-phase treatment, carbapenems are reserved for severe infections or treatment failures. For the eradication phase, Trimethoprim/sulfamethoxazole (co-trimoxazole) is preferred, and co-amoxiclav as an alternative treatment (Dance *et al*., 2014).

Good multicentre collaboration across the main endemic region of Southeast Asia and northern Australia had make incremental improvements in treating melioidosis. Instead of two phase of treatment strategy, there is most recent consensus on post exposure prophylaxis (phase 0). The type, severity and antimicrobial susceptibility of infection determined the best combination of agents used, the duration of therapy and need of adjunct modalities (Inglis *et al.*, 2010).

Treatment of melioidosis lengthy and require an intensive phase (parenteral ceftazidime, amoxicillin–clavulanic acid or meropenem) and an eradication phase (oral trimethoprim–sulfamethoxazole). Although resistance is still relatively rare, the increasing usage of antibiotics in endemic regions may compromise the therapeutic efficacies by emergence of resistance (Schweizer et al., 2012)

In a study by Crowe *et al*.(2014) in Australia, 234 isolates of *B. pseudomallei* obtained from the first positive clinical specimen from 234 consecutive patients diagnosed with melioidosis were reviewed. All isolates were sensitive to meropenem and ceftazidime. The resistance of *B. pseudomallei* to ceftazidime and/or meropenem is very rare and clinicians can be confident in the current melioidosis treatment guidelines.

2.7 ASSOCIATED FACTOR FOR MELIODOSIS OUTCOME

Melioidosis is very difficult to cure and has a mortality rate of up to 40%. Patient with a positive blood culture for *B. pseudomallei* taken at the end of the first and/or second week after hospitalization is a strong prognostic factor for death. The follow-up blood cultures in patients with melioidosis need to be highlighted (Limmathurotsakul *et al.*, 2011).

Pneumonia was the primary diagnosis for the patient with culture-confirmed melioidosis. The majority of it presented with acute or subacute presentations rather than chronic disease. According to multivariate logistic regression model, the risk factors for presentation with primary pneumonia were rheumatic heart disease or congestive cardiac failure, chronic obstructive pulmonary disease, smoking, and diabetes mellitus, with $P<.05$ for these conditions. Compared to patients with other primary presentations, those presenting with pneumonia more frequently developed septic shock (33% vs 10%; $P<.001$) and died (20% vs 8%; $P<.001$). Multilobar pneumonia occurred in 28% of patients and was associated with greater mortality (32%) than in those with single-lobe

pneumonia (14%; P<.001). Melioidosis pneumonia, particularly among those with multilobar disease is a rapidly progressive illness with high mortality. Once the risk factors have been identified, early diagnosis and treatment should be our priorities. (Meumann *et al*., 2012)

2.8 PREDICTOR FOR MELIODOSIS OUTCOME (RECOVERY)

A study by Currie *et al*.(2010), the seasonality was not a significant independent predictor of mortality. The presence of risk factors such as diabetes, hazardous alcohol use, chronic lung or renal disease and older age were the predictor of mortality from melioidosis. Diabetes as a predictor of mortality in melioidosis was also supported by Sapian *et al*.(2012).

Among those with mortality, seven were villagers and one was rescuer. The case fatality rates were higher in the villagers group which was 100% (7 out of 7) compared to 33.3% (1 out of 3) in professional rescuers. The high morbidity and mortality rate were probably due to they are relatively older, with median age of 55.5 years as compared to professional group (30 years).

In univariate analysis, risk factors for death were signs of shock or multiorgan failure (p<0.001), blood stream infection (p<0.001) and not receiving appropriate empiric therapy (p<0.001). Total of thirty (52%) patients died; 19(63%) of them died within 1

week after admission. Improvement of sepsis care and early administration of effective drugs such as ceftazidime, carbapenems, and amoxicillin/clavulanic acid are potential interventions that can decrease risk factors for death in melioidosis patients (Vlieghe *et al*., 2011).

CHAPTER 3: RESEARCH OBJECTIVES

3.1 RESEARCH QUESTION

3.1.1 How does most of melioidosis present at ED?

3.1.2 Is the initial clinical presentation and laboratory profiles predict the outcome of melioidosis?

3.2 GENERAL OBJECTIVES

To determine the predictors and outcomes of melioidosis patients presented to ED, HUSM.

3.3 SPECIFIC OBJECTIVES

3.3.1 To describe the clinical presentations and laboratory profiles of melioidosis patient presented to ED.

3.3.2 To evaluate the association of clinical presentations and laboratory profiles of melioidosis patients presented to ED and their outcomes.

3.3.3 To determine the prevalence of empirical antibiotic usage for melioidosis in ED, time lag before antimelioid therapy and association with the outcome.

3.4 NULL HYPOTHESIS

3.4.1 There was no association between the predictors (clinical presentations and laboratory profiles) of melioidosis patients presented to ED with their outcomes.

3.4.2 There was no association between the empirical antibiotic usages for melioidosis in ED and time lag before antimelioid therapy with their outcomes.

CHAPTER 4: RESEARCH METHODOLOGY

4.1 STUDY DESIGN:

A retrospective cohort study (record review)

4.2 POPULATION AND SAMPLE :

4.2.1 Source population :

- All patients presented to ED, HUSM between January 2001- December 2011 who fulfilled inclusion criteria.

4.2.2 Inclusion criteria:

- All confirmed cases of melioidosis between January 2001- December 2011 will be selected for the study.

- Attended or admitted via ED for the symptoms or sign possible related to melioidosis. The patient that culture may be taken from other health facility but attended/admitted for the same episode of melioidosis will be included in the study.

- Patient attended ED for other reason that not related to melioidosis, and no signs or symptoms can be associated with melioidosis will be included in the study if the culture were positive.

4.2.3 Exclusion criteria:

- Melioidosis patients that are not attended/admitted through ED.

- Unavailability of medical records to review.

4.3 SAMPLE SIZE

All culture positive *B pseudomallei* during study period will be included.

4.4 STUDY APPROVAL

This study was approved by Human Research Ethics Committee (HREC) Universiti Sains Malaysia on 15th January 2013 with reference to Appendix B. Consent for record tracing were obtained from Director office, HUSM on 5th February 2013 with reference to Appendix C.

4.5 DATA COLLECTION

Hospital's computerized microbiology database (WHO-net program) for candidate individuals with melioidosis, and these patients were included in this study.

4.6 DATA ENTRY AND STATISTICAL ANALYSIS

4.6.1 DATA ENTRY

Data will be entered and analysed by using SPSS version 19.0

4.6.2 DESCRIPTIVE ANALYSIS

For demographic data & clinical characteristic
Expected Result (Dummy Table)

i) Socio-demographic Data

Variables	Numerical Mean (SD)	Categorical Frequency (%)
Age		
Gender		
Race		
Occupation		
Clinical Presentation		

4.6.3 STATISTICAL ANALYSIS

Results were expressed in terms of the number and percentage or the interquartile range (IQR). For categorical variables, the differences in patient characteristics and associated factors were tested by Chi-square test. For continuous variables, the Mann-Whitney U Test was used. The p value of ≤ 0.05 was considered significant. All analyses were done using SPSS software (SPSS, Chicago, Illinois, USA) in the Medical Informatics' Laboratory, School of Medical Sciences, University Sciences Malaysia.

Objective 1:

Descriptive statistics

Objective 2:

Chi-Square, Mann-Whitney U Test, and Multiple Logistic Regression

Objective 3:

Chi-Square, Mann-Whitney U Test, and Multiple Logistic Regression

4.7 TERM DEFINITIONS

1. **Melioidosis confirmed cases**

   Culture grown from any specimen was positively identified as *B. pseudomallei.* One episode of melioidosis is presumed when the cultures were positive without normalized of clinical/laboratory symptoms or signs of infection (Wu *et al*. 2012).

2. **Bacteremia**

   The presence of bacteria in the blood that confirmed by; at least one positive blood culture from clinically septic patient (Deris *et al*.2010).

3. **Soil exposure**

   Soil exposure is defined as a contact with soil during either occupational or recreational activity such as gardening, farming, camping, or construction work (Wu *et al.* 2012).

4. **Shock**

   Shock on arrival is defined as a systolic blood pressure below 90 mmHg or a decrease of more than 30 mmHg in comparison with the patient's baseline systolic blood pressure detected at the ED, coupled with clinical evidence of peripheral hypoperfusion (Kung *et al.* 2011).

5. **Early mortality**

   Early mortality is defined as death within 48 hours after presentation at the

   ED (Kung *et al.* 2011).

6. **Sepsis**

The systemic response to infection, manifested by the presence of two or more of the conditions listed as criteria for systemic inflammatory response system (SIRS). Note: SIRS may be caused by inflammatory conditions other than infection (Peacock *et al*, 2011)

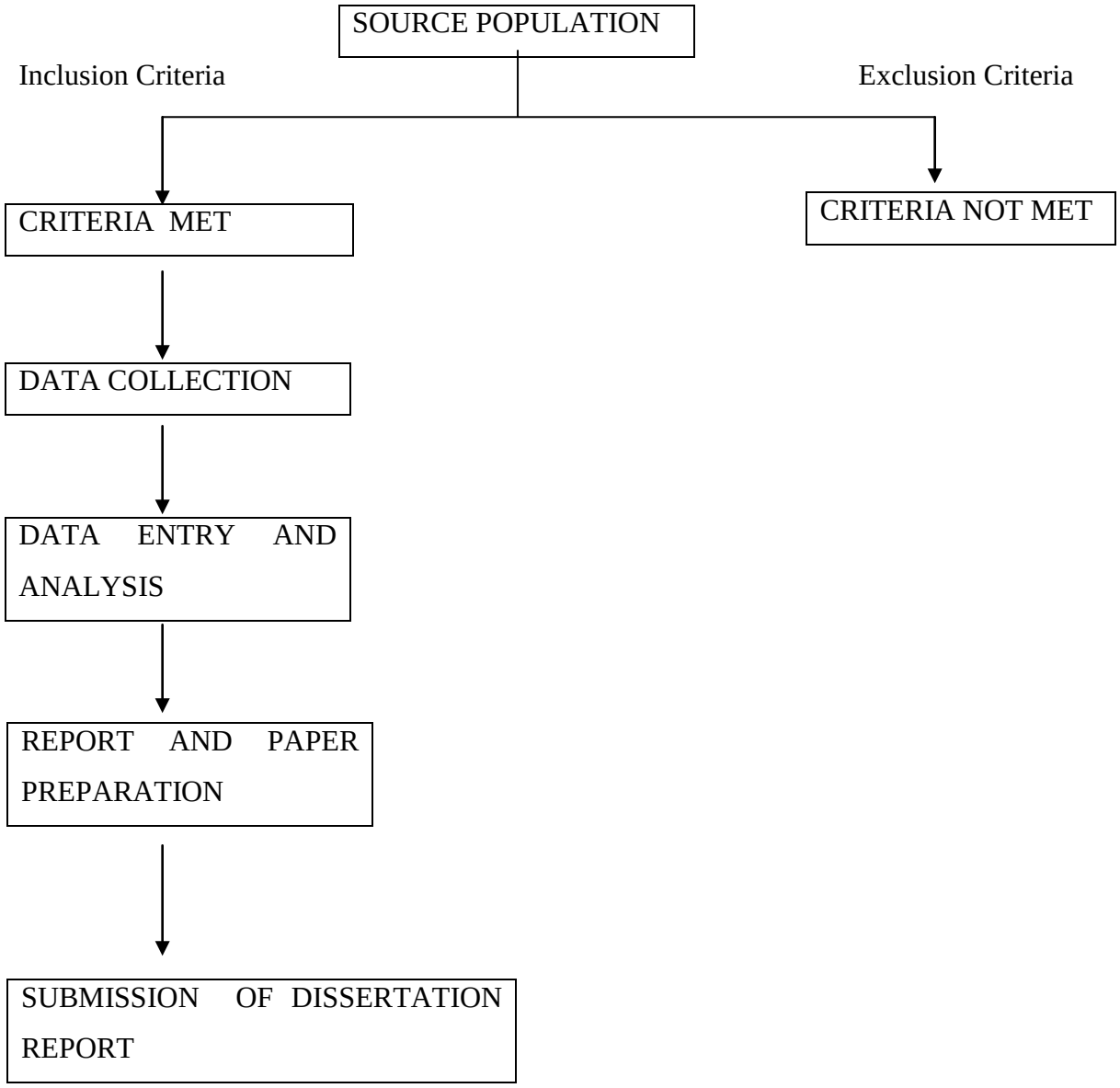
7. **Appropriate antibiotics**

Appropriate empiric antibiotic therapy at the ED was defined as the start of empiric antibiotic treatment using imipenem, meropenem, ceftazidime, amoxicillin/clavulanic acid or trimethoprim-sulfamethoxazole, which might be potentially effective against *B. pseudomallei* (Wu *et al.* 2012).

8. **Outcomes**

Either patient recovers, or death due to melioidosis, or death due to other causes. Death due to melioidosis is divided into early mortality (death within 48 hours after presentation at the ED) or late mortality (death more than 48 hours after presentation at the ED) (Kung *et al.* 2011).

4.8 FLOW CHART



CHAPTER 5: RESULTS

5.0 INTRODUCTION

Retrospectively, record of 86 patients confirmed cases by positive culture of melioidosis presented to ED HUSM, Kubang Kerian, Kelantan, Malaysia from January 2001 to December 2011 were reviewed and included in the study. Finally, data collected were analyzed using the SPSS version 19.0 software to generate the descriptive and analytical statistics.

5.1 DESCRIPTIVE ANALYSIS

5.1.1 Socio-demographic characteristics

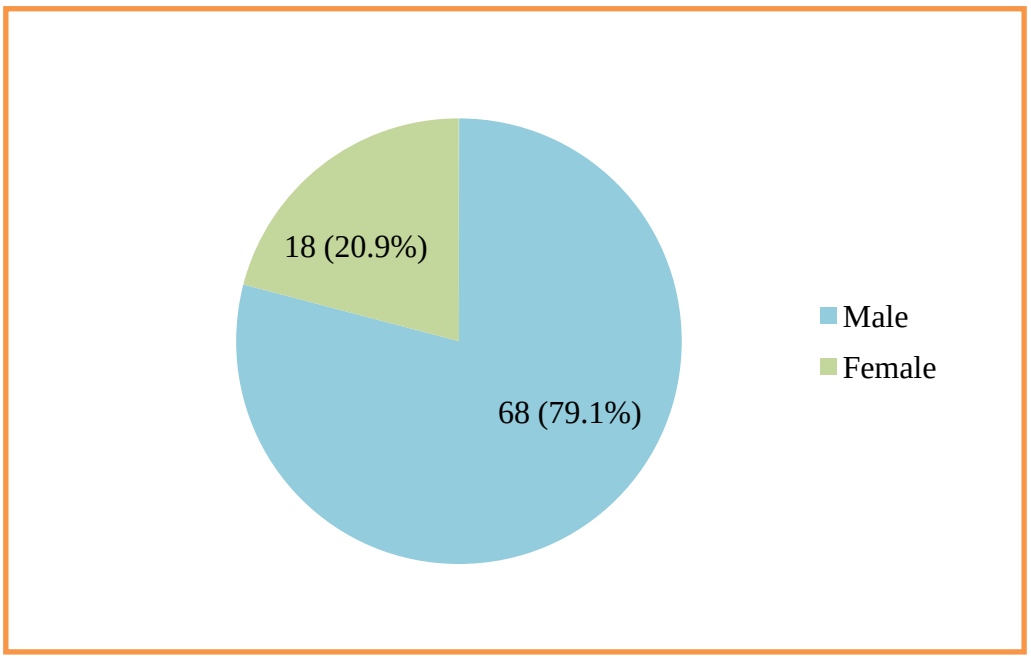


Figure 5.1 Gender distributions among the cases

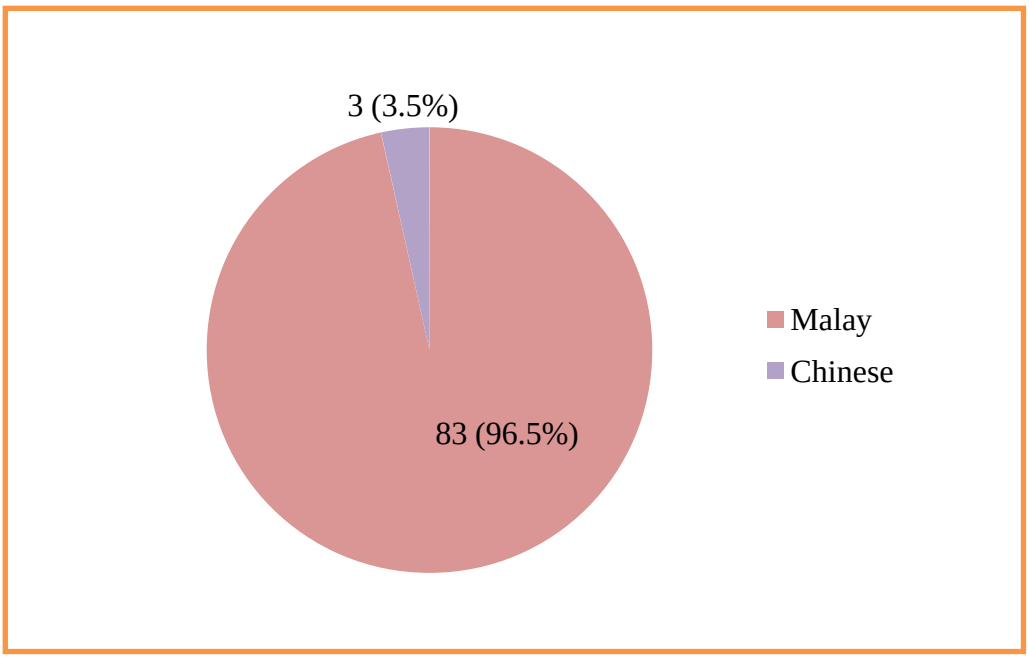


Figure 5.2 Ethnic distributions among the cases

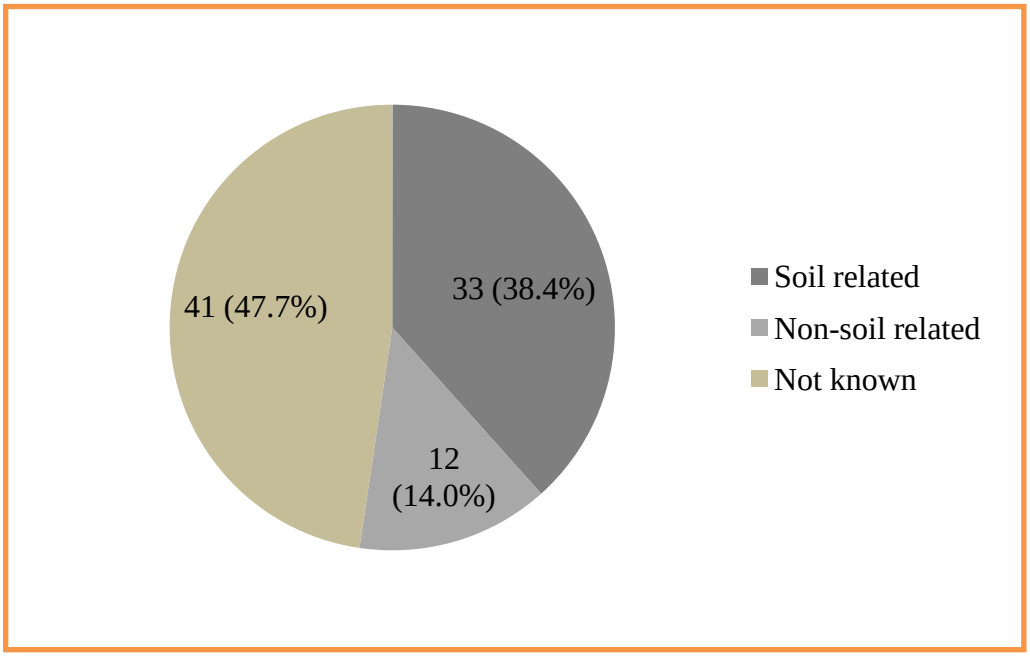


Figure 5.3 Occupation distributions among the cases

Table 5.1 Socio-demographic characteristics distribution of the patients

Characteristics	**Number (percentage) n (%)**
number of cases	86
***Age (years), median (IQR)**	51.00 (39.75,60.00)
Gender	
Male	68 (79.1)
Female	18 (20.9)
Ethnicity	
Malay	83 (96.5)
Chinese	3 (3.5)
Occupation	
Soil related	33 (38.4)
Non-soil related	12 (14.0)
Not known	41 (47.7)

*values are expressed in median (IQR)

Overall, this study involved 86 cases based on inclusion and exclusion criteria with the median age were 51 years old. Majority of the cases were male (79.1%) and based on the ethnicity, Malay contributed 96.5% of the cases and followed by Chinese (3.5%). Only 38.4% of the cases work in the soil related occupation.

5.1.2 Clinical presentations

Table 5.2 Clinical presentations of patients with melioidosis

Clinical presentations	Number (percentage) n (%)
Fever	
Yes	79 (91.9)
No	7 (8.1)
Cough	
Yes	32 (37.2)
No	54 (62.8)
Shortness of Breath	
Yes	22 (25.6)
No	64 (74.4)
Altered Mental State	
Yes	2 (2.3)
No	84 (97.7)
Seizures	
Yes	4 (4.7)
No	82 (95.3)
Urinary Tract Infection	
Yes	5 (5.8)
No	81 (94.2)
Abscess	
Yes	14 (16.3)
No	72 (83.7)
Infected wound	
Yes	2 (2.3)
No	84 (97.7)
Cellulitis	
Yes	7 (8.1)
No	79 (91.9)
Joint Pain	
Yes	4 (4.7)
No	82 (95.3)
Vomiting	
Yes	2 (2.3)
No	84 (97.7)
Diarrhoea	
Yes	1 (1.2)
No	85 (98.8)
Jaundice	
Yes	8 (9.3)
No	78 (90.7)