Infect Dis Ther
https://doi.org/10.1007/s40121-023-00768-3

ORIGINAL RESEARCH

Risk Factors for Melioidosis Mortality and Epidemics: A Multicentre, 10-Year Retrospective Cohort Study in Northern Hainan

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Received: November 29, 2022 / Accepted: January 25, 2023

ABSTRACT

Introduction: *Burkholderia pseudomallei* is a gram-negative environmental bacterium and aetiological agent of melioidosis, a tropical infectious disease with diverse clinical presentations. We aimed to describe the epidemiological and clinical characteristics of melioidosis in northern Hainan and to determine the meteorological factors affecting its morbidity.

Methods: We conducted a retrospective, multicentre, observational cohort study of 90 patients with melioidosis admitted to four general hospitals in northern Hainan from 2010 to 2020. Epidemiological, clinical presentation, laboratory and treatment outcome data were collected and analysed. The monthly incidence of melioidosis and meteorological data, including precipitation, temperature, humidity, air pressure and wind speed, for the same period were collected to analyse the relationship between meteorological factors and the incidence of melioidosis.

Results: Of the 90 patients included in the study, 79 (87.78%) were male. Patient age ranged from 10 to 81 years old, but most patients, namely, 78 (86.67%), were middle-aged and elderly people aged 41–81 years old. Forty-six patients (51.11%) were farmers. The number of cases increased significantly after 2014, with the highest numbers occurring in 2014 and 2016. The highest number of cases occurred in summer and autumn and were associated with abundant rainfall, and 58 cases (64.44%) occurred from July to December. The patients showed diverse presentations and abnormal laboratory parameters: 69 patients (76.67%) had a history of diabetes mellitus; bacteremia was present in 50 patients (55.56%), sepsis was present in 39 patients (43.33%) and pneumonia in 19 patients (21.11%). An average high-sensitivity C-reactive protein (hs-CRP) level of 149.57 ± 13.65 mg/L and a median

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Published online: 17 February 2023

procalcitonin (PCT) level of 1.31 (0.39, 6.21) ng/mL were observed. Among all the cases, 21 (23.33%) were identified as acute infections, 51 (56.67%) as subacute infections and 18 (20.00%) as chronic infections. Six patients (6.67%) died of illness; five of these patients were male, and five of these patients were middle-aged and elderly patients. The monthly average precipitation was significantly positively correlated with the monthly average incidence of melioidosis ($r = 0.74$, $P < 0.01$).
Conclusion: Male patients, farmers and especially middle-aged and elderly individuals with a history of diabetes mellitus accounted for most of the patients. The majority of cases were concentrated in coastal areas. Most cases of melioidosis occurred during the rainy seasons, and the monthly average precipitation was an independent factor affecting the average monthly incidence of melioidosis.

Keywords: Melioidosis; Meteorological factors; Epidemiological and clinical characteristics; Morbidity

Key Summary Points

Melioidosis is a tropical infectious disease caused by *Burkholderia pseudomallei*, an environmental bacterium living in contaminated soil or water.

This study aimed to provide a new insight into the epidemiology, clinical features and risk factors of melioidosis.

We found that male patients, farmers and especially middle-aged and elderly individuals with a history of diabetes mellitus accounted for most of the patients.

A regression linear model with the risk factor of precipitation was established in our study ($Y = 4.46 + 0.02X$), which is of great significance for establishing an early warning system for the prevention and control of melioidosis.

INTRODUCTION

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei* in tropical and subtropical regions and is especially prevalent in Southeast Asia and northern Australia. Humans and animals are infected via contact with water or soil contaminated with *B. pseudomallei* via inhalation, ingestion or percutaneously [1]. In China, the highest incidence is mainly concentrated in southern cities such as Guangdong, Hainan and Guangxi. Although an efficient national infectious disease reporting and surveillance network has now been established in China, melioidosis is still not included [2]. Melioidosis was detected in four US residents who did not have a history of travel to melioidosis-endemic areas but who were exposed to an aromatherapy room spray, or a component of the room spray that had been imported from India, and *B. pseudomallei* was detected in used sprays [3]. The occurrence of melioidosis is not only limited to that epidemic area but imported products and animals contaminated with *B. pseudomallei* should also be monitored [3, 4].

It is worth noting that a 2015 modeling and epidemiological study of global melioidosis morbidity and mortality by Limmathurotsakul et al. estimated that there are 165,000 human melioidosis cases per year worldwide, of which 89,000 people died, and the global mortality rate is about 90,000 per year [5]. Another 2019 study of the global burden of melioidosis estimated that disability-adjusted life years (DALYs) for melioidosis reached 4.64 million [6], which is not only higher than for intestinal nematode infections, dengue and leptospirosis but also suggests that melioidosis is an emerging neglected tropical disease [1].

B. pseudomallei has strong adaptability to the environment and can survive extreme conditions ranging from desert terrain to nutrient-free distilled water [7]. The uneven distribution of *B. pseudomallei* in epidemic areas is related to environmental factors such as temperature, rainfall, light, groundwater level and soil composition [8]. The incidence of melioidosis in northeast Thailand, the top of Australia, and Sanya, Hainan, China is mainly concentrated in the rainy season, especially after heavy rainfall or typhoons, and there is a significant correlation between incidence and precipitation [9, 10]. However, meteorological factors of precipitation and humidity in Singapore between 2003 and 2014 did not have a direct significant impact on the incidence of melioidosis [11].

B. pseudomallei can infect almost all tissues and organs of the body, causing complex and varying degrees of clinical damage [2]. The clinical spectrum of melioidosis is diverse and can be divided into different categories according to severity, including acute, subacute and chronic infection [12]. The condition of patients with acute melioidosis deteriorates rapidly, often leading to respiratory failure, multiorgan failure and shock, with a mortality rate of 19–40% [13, 14]. Chronic infection is associated with genetic variation in pathogens, adaptation to the environment and immune escape [15]. The clinical feature of chronic infection is a chronic abscess, which is very similar to that associated with tuberculosis, fungal infections or tumours [16]. Subacute infection is clinically characterised as existing between acute infection and chronic infection, with long and variable incubation periods that can last from weeks to months [12–16]. Based on the high incidence and mortality of melioidosis, the main risk factors for melioidosis must be identified, and an understanding of its clinical characteristics and prognosis for timely diagnosis and effective prevention is necessary.

METHODS

Study Population

Patients with melioidosis admitted to four general hospitals in northern Hainan from 2010 to 2020, namely, Hainan Affiliated Hospital of Hainan Medical University (Hainan General Hospital), The First Affiliated Hospital of Hainan Medical University, The Second Affiliated Hospital of Hainan Medical University, and Haikou People's Hospital, were identified. According to the inclusion and exclusion criteria, 90 patients with melioidosis in northern Hainan were included in the study. The study was approved by the Ethics Committee of Hainan General Hospital, the First Affiliated Hospital of Hainan Medical University, the Second Affiliated Hospital of Hainan Medical University and Haikou People's Hospital ([2021] No. 319).

The inclusion criteria were as follows: (1) the research subjects were living in northern Hainan, including Haikou, Wenchang, Chengmai, Danzhou, Lingao, Ding'an and Tunchang. (2) The patient data were complete. (3) The bacterial culture results of the patients were reported to be *B. pseudomallei* positive; the diagnosis was confirmed to be melioidosis, and bacterial culture specimens included blood, sputum, pus, bone marrow or urine.

The exclusion criteria were as follows: (1) the research subjects were not living in northern Hainan. (2) The subjects were inpatients without melioidosis. (3) The patient data were incomplete.

Epidemiological and Clinical Data Collection, Definition of Grouping and Definition of Treatment Outcomes

Demographic data, including sex, age, ethnicity, occupation, year and month of admission, were collected, and clinical data, including past medical history, infection sites, clinical symptoms, laboratory indicators and prognosis, were collected.

Grouping definition [12]: the patients were divided into three groups. (1) The acute infection group was defined patients whose course of disease was less than 2 weeks, with marked clinical symptoms and a very acute deterioration, often due to severe pulmonary infections causing severe impairment of respiratory function, or due to severe tissue abscesses and sepsis multiple organ dysfunction syndrome (MODS), shock, etc.; such patients were often admitted to intensive care units for monitoring. (2) The chronic infection group was defined as patients with a disease duration of more than 4 weeks, minimal symptoms and signs, a long duration of antibiotic treatment, and unremarkable radiological imaging results or patients with chronic inflammation. (3) The subacute infection group was defined as patients with an intermediate condition between the acute and chronic infection groups, with a course of 2–4 weeks.

Treatment outcome definition: cure (pathogen culture turned negative, temperature is normal, clinical symptoms basically recovered), improved (culture of pathogen turned negative, the peak temperature has decreased, clinical symptom relief), died and others (including automatic discharge for some reason, unclear treatment effect, etc.).

Meteorological Data Collection

Meteorological data from 2010 to 2020, including the monthly average precipitation, monthly average temperature, monthly average relative humidity, monthly average air pressure and monthly average wind speed, were collected from the Hainan Meteorological Bureau.

Statistical Analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS, IBM, and Chicago, USA version 22.0). Categorical data are expressed as frequencies (%), and the chi-square test or modified chi-square test was used to compare the clinical features of the three different infection groups. For numerical data, the Shapiro–Wilk test was used to test normality. Normally distributed numerical data are expressed as the mean ± standard deviation, and one-way analysis of variance (ANOVA) was used to compare the laboratory indexes of the three infection groups. Non-normally distributed numerical data are expressed as the median (interquartile range), and the Kruskal–Wallis test was used to compare the laboratory indexes of the three infection groups. The Spearman method and the stepwise forward model of multiple linear regression were used to analyse the correlation between the number of cases and meteorological factors in the corresponding month. Statistical significance was defined as a *P* value of less than 0.05.

RESULTS

Epidemiological Characteristics

Of the 90 patients with melioidosis assessed in this study, 79 (87.78%) were male. Patient age ranged from 10 to 81 years old, and 78 patients (86.67%) were middle-aged or elderly people aged 41–81 years old. Eighty-nine patients (98.89%) were of Han nationality. Forty-six patients (51.11%) were farmers. On the basis of the regional distribution of the patients, 37 patients (41.11%) were from Haikou, and 18 patients (20.00%) were from Wenchang (Table 1). Based on the temporal distribution of the cases, the number of cases from 2010 to 2013 was relatively small, and the overall trend was upwards after 2014, with the largest number in 2016. The number of cases in spring (from March to May) was 12, accounting for 13.33%; 34 cases in summer (from June to August), accounting for 37.78%; 27 cases in

Table 1 Demographic characteristics of patients with melioidosis from northern Hainan from 2000 to 2020

Variable	*N* (%)	Variable	*N* (%)
Sex		Age (years)	
Male	79 (87.78)	0–20	1 (1.11)
Female	11 (12.22)	21–40	11 (12.22)
Nationality		41–60	43 (47.78)
Han	89 (98.89)	61–81	35 (38.89)
Tu Jia	1 (1.11)		
Region		Occupation	
Haikou	37 (41.11)	Farmer	46 (51.11)
Wenchang	18 (20.00)	Staff	14 (15.56)
Danzhou	14 (15.56)	Workman	12 (13.32)
Chengmai	8 (8.89)	Retired	10 (11.11)
DingAn	7 (7.78)	Driver	2 (2.22)
Lingao	5 (5.56)	Others	2 (2.22)
Tunchang	1 (1.11)	Unknown	6 (6.67)

autumn (from September to November), accounting for 30.00%; 17 cases in winter (from December to February), accounting for 18.89%. (Fig. 1).

Clinical Characteristics

Clinical Manifestations of 90 Patients with Melioidosis

Most of the 90 patients with melioidosis presented with one or more previous medical histories: 69 patients (76.67%) had a past medical history of diabetes, 14 patients (15.56%) had cardiovascular and cerebrovascular diseases, and 12 patients (13.33%) had chronic hepatobiliary diseases. The sites of infection were as follows: 60 cases (66.67%) in the blood, 39 (43.33%) in the lung and 20 (22.22%) in the liver and spleen. Fifty patients (55.56%) presented with bacteremia, followed by 39 patients (43.33%) with sepsis and 19 patients (21.11%) with pneumonia (Table 2).

Comparison of Clinical Characteristics Among Three Infection Groups with Melioidosis

Among all cases, 21 (23.33%) were acute infections, 51 (56.67%) were subacute infections and 18 (20.00%) were chronic infections. There were no significant differences in patient sex, age,

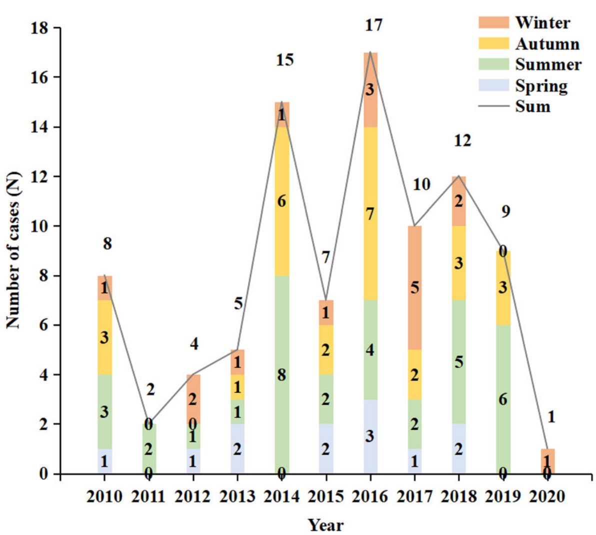

Fig. 1 Annual and monthly distribution of melioidosis in northern Hainan from 2000 to 2020

Table 2 Clinical characteristics of 90 patients with melioidosis in northern Hainan from 2010 to 2020

Variable	Number	Percent
Past medical history		
Diabetes	69	76.67
Cardiovascular and cerebrovascular diseases	14	15.56
Chronic hepatobiliary diseases	12	13.33
Chronic kidney diseases	5	5.56
Tuberculosis	5	5.56
Others	5	5.56
Infected organs		
Blood	60	66.67
Lung	39	43.33
Liver and spleen	20	22.22
Bone	6	6.67
Others	5	5.56
Clinical manifestations		
Bacteremia	50	55.56
Sepsis	39	43.33
Pneumonia	19	21.11
Organ abscess	17	18.89
Others	4	4.44
Treatment outcome		
Cure	9	10.00
Improved	57	63.33
Died	6	6.67
Others	18	20.00

occupation, or region among the three groups ($P > 0.05$). Most patients had a fever, and the body temperature was between 36 0.00 and 43.00 °C on admission, with an average of 38.08 ± 0.12 °C.

Of the patients with acute infection, 19 (90.48%) had a previous medical history. Forty-

Table 3 Comparison of clinical characteristics of three melioidosis infection groups in northern Hainan from 2010 to 2020

Variable	All ($N = 90$) Frequency, n (%)	Type of infection			χ^2	P
		Acute ($N = 21$) Frequency, n (%)	Subacute ($N = 51$) Frequency, n (%)	Chronic ($N = 18$) Frequency, n (%)		
Past medical history						
Yes	71 (78.89)	19 (90.48)	42 (82.35)	10 (55.56)[a,b]	7.03	0.03
No	19 (21.11)	2 (9.52)	9 (17.65)	8 (44.44)[a,b]		
Number of infected organs						
1	36 (40.00)	2 (9.52)	21 (41.18)[a]	13 (72.22)[a,b]	23.85	< 0.01
2	37 (41.11)	9 (42.86)	23 (45.10)[a]	5 (27.78)[a,b]		
≥ 3	17 (18.89)	10 (47.62)	7 (13.73)[a]	0 (0.00)[a,b]		
Types of clinical manifestation						
1	48 (53.33)	3 (14.29)	31 (60.78)[a]	14 (77.78)[a]	28.41	< 0.01
2	24 (26.67)	6 (28.57)	15 (29.41)	3 (16.67)		
≥ 3	18 (20.00)	12 (57.14)	5 (9.80)[a]	1 (5.56)[a]		

[a]Compared with the acute infection group, $P < 0.05$
[b]Compared with the subacute infection group, $P < 0.05$

two patients (82.35%) with subacute infection had a previous medical history. Ten patients (55.56%) with chronic infection had a previous medical history. The proportion of patients with acute and subacute infections with a previous medical history was higher than that with chronic infection ($P < 0.05$).

Regarding the infected organs, there were 54 cases (60.00%) with two or more infected organs. Most cases with three or more infected organs were acute cases. There were 10 acute cases (47.62%) with three or more infected organs, which was higher than those in the subacute and chronic groups ($P < 0.05$).

Acute infections often involve multiple organs and cause multiple clinical manifestations. Most acute infections have three or more clinical manifestations. There were 12 acute cases (57.14%) with three or more clinical symptoms, which was higher than that in the subacute group and the chronic group ($P < 0.05$) (Table 3).

In the acute infection group, the average high-sensitivity C-reactive protein (hs-CRP) level was 249.21 ± 165.75 mg/L, the average hs-CRP level associated with acute infection was higher than those of subacute infection and chronic infection ($P < 0.05$) and the average hs-CRP level of subacute infection was higher than that of chronic infection ($P < 0.05$). The median procalcitonin (PCT) value in the acute infection group was 21.88 (1.31, 35.19) ng/mL, which was higher than those in the subacute and chronic infection groups ($P < 0.05$) (Table 4).

Bacterial Culture and Treatment Outcome

Of the 74 positive reports based on complete culture, 41 were identified in blood samples (55.41%), 20 in sputum samples (27.03%), 10 in pus samples (13.51%), 1 in a pleural effusion sample (1.35%), 1 in an ascites sample (1.35%) and 1 in placental drainage solution (1.35%).

Table 4 Comparison of the laboratory test index results in the three infection groups

Variable	Sum of cases (N = 90)	Type of infection			F or H	P
		Acute (n = 21)	Subacute (n = 51)	Chronic (n = 18)		
Admission temperature (°C)	38.08 ± 0.12	38.72 ± 1.18	38.12 ± 0.87[a]	37.21 ± 1.05[a,b]	10.17	< 0.01
White blood cell count (× 10^9/L)	10.89 ± 0.60	13.13 ± 6.86	12.89 ± 7.45	11.92 ± 3.95	0.59	0.94
hs-CRP (mg/L)	149.57 ± 13.65	249.21 ± 165.75	176.06 ± 125.11[a]	83.81 ± 93.32[a,b]	7.67	< 0.01
Erythrocyte sedimentation rate (mm/h)	70.01 ± 5.60	63.33 ± 11.43	67.24 ± 6.76	79.75 ± 12.92	0.67	0.52
PCT (ng/mL)	1.31 (0.39, 6.21)	21.88 (1.31, 35.19)	1.33 (0.50, 3.02)[a]	0.06 (0.04, 0.23)[a]	13.75	< 0.01

[a]Compared with the acute infection group, $P < 0.05$
[b]Compared with the subacute infection group, $P < 0.05$

Among the 90 patients, 9 were cured (10.00%), 57 were improved (63.33%), 6 died (6.67%), and 18 were others (20.00%) (Table 2).

Clinical Features of Patients Who Died

Six patients (6.67%) died; five were male, and five were middle-aged and elderly patients. Five patients had acute infections. All patients who died had a past medical history of diabetes mellitus and presented with two or more infected organs.

Risk Factors for Mortality Rate

Correlation Analysis Among Meteorological Factors

There was a positive correlation between precipitation and air temperature ($r = 0.83$, $P < 0.05$), air temperature and air pressure ($r = -0.85$, $P < 0.01$), air temperature and wind speed ($r = -0.85$, $P < 0.01$) and temperature and wind speed ($r = 0.62$, $P < 0.05$), and air pressure was negatively correlated with precipitation ($r = -0.78$, $P < 0.01$). Among these findings, the correlation between air temperature and air pressure was the strongest.

Correlation Analysis of Monthly Mortality Rate and Meteorological Factors

From 2010 to 2020, the average precipitation in August was the highest, the average relative humidity in January was the highest, the air pressure fluctuation was not large, the average air pressure in September was the lowest, the highest wind speed was in January and the lowest was in August. There was a significant positive correlation between the monthly average precipitation and the monthly cases ($r = 0.72$, $P < 0.01$). There was no significant correlation between the monthly cases and the average temperature, average relative humidity, average air pressure or average wind speed ($P > 0.05$) (Fig. 2).

Multiple Linear Regression Analysis of Monthly Cases and Meteorological Factors

The average precipitation was an independent factor affecting the monthly average incidence ($P < 0.05$), and the greater the precipitation was, the higher the monthly average incidence. The following regression equation of the incidence number Y and the average precipitation X was established: $Y = 4.46 + 0.02X$ (Fig. 3).

Fig. 2 Correlation of the five meteorological factors in northern Hainan between 2010 and 2020. **a** Wind speed, **b** average air pressure, **c** average relative humidity, **d** average temperature, **e** monthly average precipitation

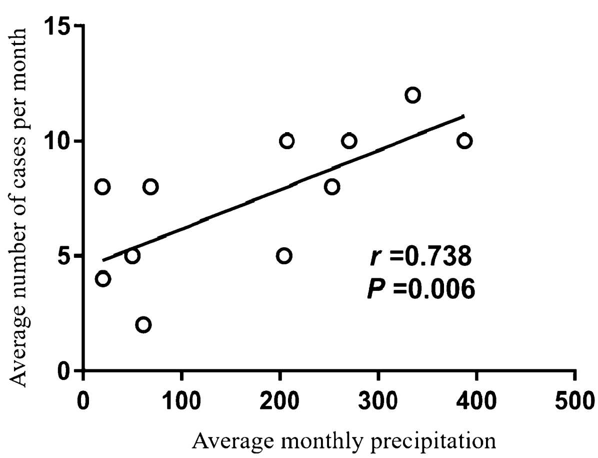

Fig. 3 Linear regression between the number of cases of melioidosis and the average monthly precipitation

DISCUSSION

Melioidosis is a zoonotic disease caused by *B. pseudomallei*, and there are approximately 165,000 cases of melioidosis and 89,000 deaths worldwide every year [5]. Diabetes is one of the risk factors for the onset of melioidosis; other factors include being a farmer who is often in contact with soil or water (especially in the rainy season), being a man over 45 years old, drinking excessively, having chronic liver disease, chronic lung disease, chronic kidney disease and other comorbidities, and using hormones long term [15, 16]. In our study, the majority of patients were male (87.78%), aged over 41 years and farmers (51.11%). Most patients had a past medical history, including diabetes (76.67%), cardiovascular and cerebrovascular diseases (15.56%) and chronic hepatobiliary diseases (13.33%). Patients with diabetes are three times more likely to develop melioidosis than patients without diabetes, which is related to the fact that hyperglycaemia can damage neutrophils and lymphocytes and destroy phagocytes and immune function. As persistent hyperglycaemia further worsens the condition of melioidosis, the aggravation of melioidosis also leads to poor blood sugar control, forming a vicious cycle [17, 18]. Most of the cases in our study also occurred in coastal areas and during the rainy season in summer and fall, which is consistent with the case reports in Hainan, China [19, 20]. In our study, we have observed a sharp increasing in the number of cases after 2014, reasons for which may be for the increased awareness of melioidosis, improvement of *B. pseudomallei* detection technology and higher level of diagnosis of melioidosis. In addition, the frequency of typhoons in 2014 was also higher than in previous years. Hence, it is necessary to pay attention to susceptible people and monitor melioidosis in rainy and typhoon seasons.

Melioidosis occurs primarily through wound contact with soil and water contaminated with *B. pseudomallei* or through infections of the digestive tract and respiratory tract. *B. pseudomallei* can infect a variety of organs, resulting in various clinical features, which complicates clinical diagnosis and treatment; thus, misdiagnosis is common [15, 21]. In our study, the infection sites mainly included the blood, lung, liver and spleen. Bacterial culture is the main criterion for the diagnosis of melioidosis [15]. Among 74 complete positive reports of bacterial culture, the culture samples were mainly blood, sputum and pus. As a result of the immune escape of *B. pseudomallei*, the changed incubation period, the difference in the number of bacteria in the tissue, and the interference of other pathogens on bacterial culture, multitissue and repeated bacterial culture can prevent a missed diagnosis [22, 23]. A positive case of placental drainage was also found, and in the past, there were similar rare cases of neonatal transmission through breastfeeding and premature birth caused by pregnancy-associated infections [24, 25].

In terms of the course and severity of melioidosis, it can be divided into acute, subacute, chronic, latent or asymptomatic infections or into primary local melioidosis and disseminated melioidosis, and formulating the corresponding diagnosis and treatment measures according to the classification of different infections is conducive to the prognosis of melioidosis [12, 14, 15, 26]. In the 90 patients with melioidosis described here, the reported rates of acute, subacute and chronic infection were 23.33%, 56.67% and 20.00%, respectively. In 21 cases of acute infection, multiple organs were usually affected, with moderate to high fever, mainly manifested as severe blood sepsis, severe pneumonia, organ and function failure, and laboratory abnormalities such as in the levels of hs-CRP and PCT. Acute infections are mostly multifocal and often blood-transmitted, leading to sepsis, multiple organ abscesses, MODS and shock. The mortality rate of acute infection is much higher than that of chronic infection. Therefore, timely anti-infection treatment should be performed, emphasis should be placed on organ support treatment and abscesses should be drained in a timely manner to improve immunity [12, 15, 27]. In the chronic infection cases studied here, there were usually one to two infected organs, and the course of the disease progressed slowly, manifesting as chronic inflammatory manifestations similar to tuberculosis, tumours and fungal infections, which was consistent with previous studies [27, 28]. Patients with chronic infections have poor treatment compliance, and attention should be given to the recurrence of melioidosis [29, 30]. Subacute infection cases are clinically characterised by variable latencies, which can last from weeks to months and can induce mild and moderate blood sepsis, local abscess and pneumonia [12, 15, 26, 31]. Whether subacute or chronic, it can be converted into an acute infection when immunity is low and the bacterial count increases rapidly [12, 15, 26–28, 31].

In our study, six patients (6.67%) died of illness during hospitalisation, with a mortality rate lower than the 10–40% reported in previous studies [5, 17, 19]. This was related to the increasing awareness of melioidosis and to the poor follow-up after the automatic discharge of some patients with worsened disease in our study due to local cultural customs and economic reasons. The patients who died were mainly middle-aged and elderly men with a past history of diabetes. It has been reported previously that death due to melioidosis is more common in elderly individuals and is associated with immunodeficiency [29, 30, 32]. In the current study, most of the patients who died had acute infections and multiple infected organs. We speculate that the haematogenous spread of *B. pseudomallei* led to sepsis in most patients, causing organ failure and shock leading to death. In addition, sepsis, shock, renal failure, hypoproteinaemia and hs-CRP > 100 IU/L have also been reported as risk factors for death and poor prognosis [1, 32].

Meteorological factors such as precipitation, temperature, humidity, air pressure and wind speed have an impact on various physiological and metabolic functions of the human body, such as thermoregulation, hot and cold sensation, cardiovascular function, and metabolism. In addition, meteorological factors are related to the spread of infectious diseases [33, 34]. Australian scholars analysed the association between melioidosis cases and weather events from 1990 to 2013, and the results showed that dew point, cloud cover, rainfall, maximum temperature, and groundwater increase were associated with an increased risk of melioidosis [8]. Malaysian scholars conducted a retrospective analysis of 145 cases of melioidosis and showed a positive association between cases and deaths and monthly rainfall [7]. Our study found that the precipitation in Hainan increased with increasing temperature, while the air pressure and wind speed decreased with increasing temperature. However, 37–42 °C is the most suitable growth temperature for *B. pseudomallei*. When the temperature is high, the probability of *B. pseudomallei* replication increases, and the high temperature is accompanied by strong precipitation, which makes the bacteria spread in the soil or paddy field, increasing the risk of *B. pseudomallei* infection. Zhu and Kuang analysed the correlation between melioidosis and meteorological factors in Sanya, Hainan, from 2013 to 2017. The results showed that climatic factors in Sanya were an important factor affecting the incidence of melioidosis, and precipitation and wind speed were positively correlated with the number of cases [35]. Different from the results of the study in Sanya, we found that only precipitation was significantly correlated with the number of cases. Hainan has a typical tropical monsoon climate, but there are certain differences in meteorological factors between the north and the south. The distribution of maximum wind speed varies in different seasons in each region, but the maximum precipitation occurs in summer [36]. Therefore, whether the wind speed index affects the transmission of melioidosis needs further research.

We also found that the cases of melioidosis were mainly concentrated in summer and autumn, which are the rainy seasons in Hainan, and precipitation had the greatest impact on the spread of melioidosis. The greater the precipitation is, the greater the monthly average number of cases. This is consistent with the conclusions of other studies [37]. Therefore, a consensus guideline on soil sampling for *B. pseudomallei* was proposed in 2013, stating that *B. pseudomallei* is most abundant in soils at a depth of at least 10 cm from the surface; during the rainy season, *B. pseudomallei* can migrate from deeper soil layers to the surface and replicate [38]. However, since a melioidosis vaccine has not yet been developed and a sound early warning system has not been established, *B. pseudomallei* in the environment should be monitored in areas with a high incidence of melioidosis, and an early warning system should be established for precipitation.

A study reported that during the Taiwa, China typhoon month, the typhoon was positively correlated with environmental *B. pseudomallei* concentrations, while the wind speed was negatively correlated with environmental *B. pseudomallei* concentrations [39]. From July to September 2005, 40 cases of melioidosis were diagnosed in southern Taiwan, China after the typhoon [40]. The number of patients with melioidosis admitted to a hospital in Hainan in 2014 over the course of 2 months after Typhoon Rammasun increased sharply by 129% [41]. We also found a threefold increase in the number of cases of melioidosis in 2014 relative to 2013. In 2016, the number of cases was also relatively high. In October 2016, Salija, which landed in Wanning, Hainan, in October 2016, became the strongest typhoon to make landfall in Hainan since October 1970, and typhoons and heavy rainstorms in 2016 increased compared with previous years. The reason may be related to the typhoon season. The typhoon itself usually does not cause the spread of infectious diseases, but it

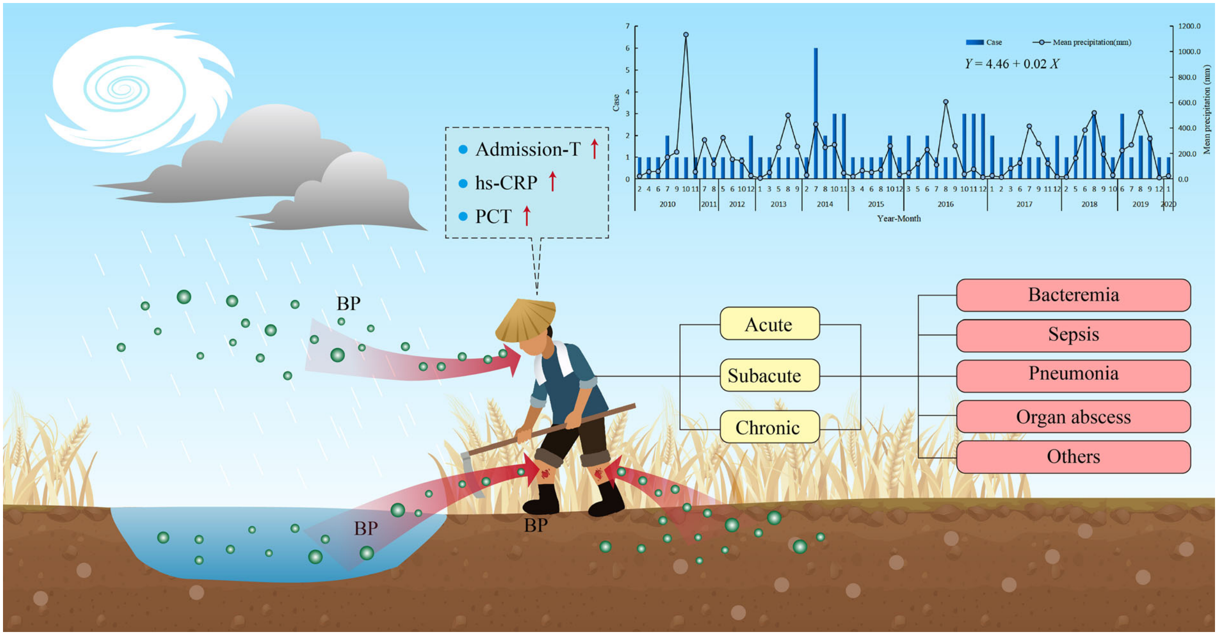

Fig. 4 Summary graph of this study

can increase the potential of disease transmission under specific circumstances [42]. Typhoons are accompanied by heavy precipitation, which makes *B. pseudomallei* in the soil diffuse, which increases not only the scope of pollution but also the probability of aerosol inhalation or inhalation events such as drowning after heavy rainfall and strong storms and may increase the amount of inhalation, resulting in patients with a higher risk of pneumonia manifestations, septic shock and death [16].

However, our study is an observational one with limited causal inferences about the factors leading to the occurrence of and death due to melioidosis. There may be many missed diagnoses in addition to the inclusion of confirmed subjects, and we have only included cases of melioidosis in northern Hainan. Therefore, monitoring the occurrence of melioidosis cases in the whole Hainan area, following up on the recurrence of melioidosis cases, and further identifying the environmental factors of melioidosis and the risk factors for death from melioidosis will be our next work. We will also investigate research on melioidosis related to molecular biology, pathogenic mechanisms, rapid detection methods and vaccine development.

CONCLUSION

This study focused on the risk factors for melioidosis, mainly analysing the correlation between melioidosis and meteorological factors. In addition, the influence of clinical manifestations and medications on the prognosis of patients with melioidosis was analysed. We have established a regression linear model with the risk factor of precipitation, which is of great significance for establishing an early warning system for the prevention and control of melioidosis (Fig. 4). Additionally, we believe that patients with melioidosis should be diagnosed in a timely manner and treated with antibiotics to prevent organ failure, which is the key to a good prognosis.

ACKNOWLEDGEMENTS

The authors sincerely thank the staff of the study sites and those involved in data collection, including Hainan General Hospital, the First Affiliated Hospital of Hainan Medical University the Second Affiliated Hospital of Hainan Medical University, Haikou People's Hospital and Hainan Medical University. The authors would also like to acknowledge the Hainan Meteorological Bureau for their provided meteorological data.

Funding. Hainan Province Philosophy and Social Science Planning project (HNSK(ZC)20-36), Cultivation Project 530 of Hainan General Hospital (2021MSXM11). Hainan General Hospital is also funding the journal's Rapid Service fee.

Editorial Assistance. Editing assistance was provided by Springer Nature Author Services.

Author Contributions. Data collection and analysis, writing (original draft): Wanting Zheng and Chengwang Zhong; Data verification: Xiao Sha and Shicheng Kuang; Conceptualisation, project administration, funding acquisition, and writing (review): Xiao Sha and Biao Wu. All authors contributed to the article and approved the submitted version. All authors read and approved the final manuscript.

Disclosures. All named authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Compliance with Ethics Guidelines. Hainan General Hospital Ethics Committee, the First Affiliated Hospital of Hainan Medical University Ethics Committee, the Second Affiliated Hospital of Hainan Medical University Ethics Committee, and Haikou People's Hospital Ethics Committee all approved this study and consent to participate ([2021] No. 319). Patients, or the family members of those who have passed away provided consent. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The data sets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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