Original Article

Clinical Profile and Predictors of Mortality among Patients with Melioidosis

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Abstract

Introduction: Melioidosis is an under-recognized but important infection with high mortality and morbidity. It is endemic along the coastal regions of the Southern part of India. The present study focuses on the varied clinical manifestations, associated risk factors, and outcomes in patients from the Southeastern part of India. **Methods:** Seventy patients from January 2018 to June 2021 from a Tertiary Care Hospital were included and prospectively followed up from 6 months to 3 years. Cox regression was performed to test for the association of various clinical and demographic factors with overall survival. **Results:** Diabetes and occupational exposure to soil and water (78.6%) followed by alcoholism (61.4%) were the most common risk factors for melioidosis. The most frequent presentation was sepsis (47.1%), followed by skin and soft tissue infection (32.9%) and pneumonia (25.7%). Mortality was 50%. Patients with sepsis had a 3.5-fold higher risk of mortality (adjusted hazard ratio = 3.50; $P = 0.01$) while other risk factors were not significantly associated with mortality. **Conclusion:** Lifestyle-dependent risk factors (diabetes, occupational exposure, and alcoholism) were most common among patients with melioidosis. Hospitalization among patients with sepsis is associated with high mortality despite the initiation of specific therapy.

Keywords: Burkholderia pseudomallei, melioidosis, mortality, risk factors, treatment

Introduction

Melioidosis is a potentially life-threatening infection caused by soil-dwelling Gram-negative bacilli, *Burkholderia pseudomallei*. It can cause either localized infection such as pneumonia, arthritis, abscesses, or systemic dissemination leading to sepsis. The presentation may be acute, chronic, fulminant, or indolent.[1] Early recognition and prompt initiation of antibiotics are essential for survival. Melioidosis is endemic to South East Asia and Northern Australia.[1] Most of the data on melioidosis from India comprises case series and a few retrospective single-center studies.[1-3] Puducherry, being a coastal region, has had sporadic cases of melioidosis in the past.[4,5] Therefore, a prospective study of laboratory-confirmed cases of melioidosis was carried out to document varied clinical manifestations and identify the factors associated with overall survival (OS) in melioidosis patients.

Methods

This is a prospective study of 70 laboratory-confirmed melioidosis cases admitted to a Tertiary Care Institute in Southern India, from January 2018 to June 2021. The objective was to describe the clinical profile of confirmed cases; hence, the sample size was not calculated. The approval was obtained from Institutional Ethics Committee (JIP/IEC/2018/0230) for Human Studies and was conducted in accordance with the Declaration of Helsinki. During the study, the authors followed applicable EQUATOR Network guidelines. The clinical presentation, risk factors, treatment details, outcome, occupation and other sociodemographic details were recorded in a structured pro forma using Microsoft Excel. Specimens for microbiological investigations were processed as per standard procedures.[6] Isolates were confirmed by VITEK 2 system (bioMèrieux, Marcy-l'Étoile, France) and polymerase chain reaction targeting a Type III secretion

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system gene cluster (TTS1).[7] Most patients were followed up telephonically, for a minimum period of 6 months and a maximum of 3 years. The patients or their relatives were contacted to avoid a loss to follow-up.

Definitions

Acute presentation - symptoms present for <2 months.[8]

Chronic presentation - symptoms present for more than 2 months.[8]

Sepsis - patients with features of sepsis (hyper/hypothermia, leukocytosis, hypotension, pulse rate >90/min, respiratory rate >18/min) and isolation of *B. pseudomallei* from any clinical specimen.[9]

Excessive alcohol consumption - alcohol consumption of more than 14 standard drinks/week or 4 drinks/day for men and more than 7 standard drinks/week or 3 drinks/day for women in accordance with the criteria established by the US National Institute on Alcohol Abuse and Alcoholism.[10]

Superficial abscesses - abscesses involving skin and soft tissues.

Deep organ abscess - abscess involving organs such as the brain, lungs, liver, spleen, prostate, etc.

Anti-melioidosis treatment comprises initial intensive therapy and eradication therapy.

The treatment of choice for the initial intensive therapy is intravenous ceftazidime (50 mg/kg up to 2 g) every 8 h or meropenem (25 mg/kg up to 1 g) every 8 h for a duration of 10–14 days. The treatment for eradication therapy is for a minimum of 12 weeks with co-trimoxazole (first choice) 160/800 mg tablets; two tablets every 12 h and co-amoxiclav or doxycycline 100 mg; twice a day is the second choice.[11-13]

Statistical analysis

The baseline characteristics were reported using descriptive statistics: categorical variables such as gender, occupation, chronic kidney disease (CKD), and diabetics were summarized as frequencies and percentages. The age which followed normal distribution was expressed as mean with standard deviation, whereas the variables that do not follow normal distribution such as duration of onset of symptoms to admission, admission to reporting, admission to start of specific therapy, and hospital stay were summarized using median along with the first and third quartiles (Q1, Q3). Kaplan–Meier method was used to plot the survival curve and log-rank test was used for the comparison of survival functions across different groups. Univariate Cox regression was used to find the demographic and clinical factors associated with OS. OS was defined as the time from a clinical diagnosis of melioidosis to death. Unadjusted hazard ratios (HR) along with their 95% confidence intervals (CI) were reported. The variables which were found to be significant predictors of mortality in the Univariate analysis were included in the multivariable Cox regression and adjusted HR along with their 95% CI were reported. All statistical analyses were performed using SPSS software version 19.0 (IBM; Armonk, NY, 112 USA) and R software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria,2021) at 5% level of significance. $P < 0.05$ was considered to be statistically significant.

Results

Patient demographics

All the patients with melioidosis reported during the study were included (males $n = 63$, 90%). The mean age was 47.56 (14.55) years, with four children (10–14 years). There were 42 farmers (60%) and an additional 13 patients ($n = 55$, 78.6%) had occupational exposure to soil and water. Among the 13 patients, 4 were fishermen and 9 were construction workers [Table 1].

Presenting symptoms and clinical course

Fever was the most common presenting symptom and was present in 60 (85.7%) patients, followed by cough and presence of abscesses in 23 (32.9%), breathlessness in 22 (31.4%), abdominal pain in 18 (25.7%), altered sensorium in 17 (24.3%), and joint pain in 15 (21.4%) patients (some patients had more than one presenting symptoms).

Sixty-five (92.9%) patients had acute presentation while 5 (7.1%) had a chronic presentation. The median duration of symptoms before presentation, from date of admission to diagnosis (isolation of *B. pseudomallei*) and start of specific therapy were 12 days (Q1, Q3; 5, 30 days), 3 days (Q1, Q3; 2, 4 days) and 3 days (Q1, Q3; 1, 6 days), respectively.

Table 1: Sociodemographic details and risk factors for melioidosis patients ($n=70$)

Sociodemographic details and risk factors	Males (63)	Females (7)
Age (years)		
1–15	4	0
16–35	6	1
36–49	25	2
≥50	28	4
Occupation		
Farmers	38	4
Construction workers	9	0
Fishermen	4	0
Carpenters	3	0
Others*	8	0
Unemployed	1	3
Risk factors		
Diabetes mellitus	49	6
Environmental exposure (soil/water)	51	4
Age 50 or above	28	4
Alcoholism	43	0
CKD	8	1
Renal transplant recipient	0	1
Absence of risk factors	4	1

*Teacher, students, auto drivers, and peanut vendor. CKD: Chronic kidney disease

There were 47 (67.1%) bacteremic patients [Table 2]. Sepsis was present in 33 (47.1%) patients. Thirty-eight patients received meropenem and 20 patients received ceftazidime in intensive phase with an average duration of 26 days in the meropenem group and 14 days the in ceftazidime group. Twenty patients received cotrimoxazole and ten patients received doxycycline and three received a combination of cotrimoxazole and doxycycline in the continuation phase with 90 days. The median duration of hospital stay was 15 days (Q1, Q3; 3, 26 days).

Overall mortality was 50%. Of these, ten patients expired before initiation of treatment while 24 deaths occurred during treatment. One patient had a relapse and expired during the second admission. Mortality was higher in patients with sepsis compared to patients without sepsis [Table 3]. About two-thirds (66%) of patients with bacteremia progressed to sepsis.

Pulmonary melioidosis accounted for 19 (27.1%) cases, (pneumonia alone 17, lung abscess alone 1, both pneumonia, and lung abscess 1) and 13 deaths [Tables 2 and 3]. Twenty-four patients had deep organ abscesses with spleen and liver being the most common sites. Septic arthritis was seen in 15 patients and osteomyelitis was seen in one patient [Tables 2 and 3]. Polyarthritis was present in five patients. Eleven of the 15 patients were bacteremic and five had septic shock. Infection was fatal in 10 of the 15 patients with septic arthritis [Table 3]. Seven (10%) patients (5 adults and 2 children) presented with neurological melioidosis of whom three had brain abscess, three had encephalitis, and one presented with myelitis [Table 2]. Melioidosis was suspected only in 12 (17.1%) patients on presentation. Community-acquired pneumonia, tuberculosis, septic shock of unknown cause, cerebral mucormycosis, and infected pancreatic pseudocyst were the other initial diagnoses.

Factors for predicting mortality

Diabetes and environmental exposure to soil/water (n = 55, 78.6%) were the most common risk factors for melioidosis followed by alcoholism (n = 43, 61.4%) [Table 1].

Table 2: Clinical details of melioidosis patients (n=70)

Clinical details	n (%)
Bacteremia	47 (67.1)
Sepsis	33 (47.1)
Pneumonia	18 (25.7)
Skin and soft tissue	23 (32.9)
Intra-abdominal abscesses	12 (17.1)
Lung abscess	2 (2.9)
Prostatic abscess	4 (5.7)
Renal abscess	1 (1.4)
Parotid abscess	1 (1.4)
Brain abscess	3 (4.3)
Tubo ovarian abscess	1 (1.4)
Osteomyelitis/septic arthritis	16 (22.9)
Neurological disease	7 (10)

A few patients had multiple presentations

Among the various factors studied to predict the risk of death, presence of bacteremia increased the risk of death from melioidosis by 7.89-fold (unadjusted HR: 7.89, 95% CI: 2.41, 25.87, P = 0.001), compared to nonbacteremic melioidosis [Table 4]. Likewise, patients with sepsis had 6.19-fold higher risk of mortality (unadjusted HR: 6.19, 95% CI: 2.79, 13.73, P < 0.001) compared to patients without sepsis. However, age of 50 years or above, male gender, and the presence of any one risk factor or their absence did not influence the outcome [Table 4].

In the multivariable Cox regression analysis, only sepsis was found to be an independent predictor when adjusted for bacteremia (adjusted HR = 3.50; 95% CI: 1.44, 8.54, P = 0.01) [Table 4].

A log-rank test revealed that patients without bacteremia survived better when compared to patients with bacteremia [P < 0.001, Figure 1]. Likewise, better survival was noted in patients without sepsis compared to patients who had sepsis [P < 0.001, Figure 2].

Discussion

Melioidosis is an emerging infectious disease in the tropics and is caused by *B. pseudomallei*. Exposure to soil and water harboring *B. pseudomallei* is considered one of the risk factors for acquiring this disease.[14] In the present study, 78.6% of the patients were farmers, fishermen, or manual laborers with occupational exposure to soil or water.

Pneumonia is the most common clinical presentation in other studies from endemic regions.[1,8,9,15] In contrast, pneumonia accounted for only 25.7% in the present study similar to a study by Koshy *et al*., with 24.5% lung involvement.[2] Half of the 18 melioidotic pneumonia cases occurred during the monsoon months. The mode of acquiring acute melioidotic pneumonia is attributed to a shift toward inhalation, during heavy rains and cyclones.[1,14,16]

Single/multiple abscesses of skin and internal organs are common presentations and are acquired by inoculation of *B. pseudomallei* through broken skin or through hematogeneous spread.[17] The incidence of skin and soft tissue infection varies from 13.1% to 48.4%.[2,4] The present study had 23 (32.9%) cases of skin and soft tissue infection.

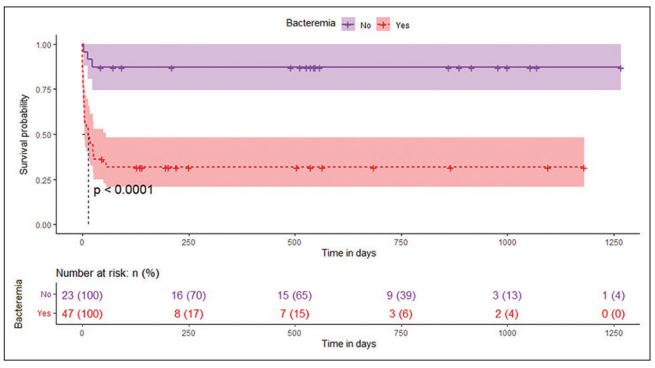

Figure 1: Kaplan–Meier survival plots of patients stratified by bacteremia

Table 3: Clinical presentation and outcome in sepsis and nonsepsis melioidosis patients

Clinical presentation*	Total (70%), *n* (%)	Deaths (35%), *n* (%)	Sepsis 33		Nonsepsis 37	
			n (%)	Deaths (%)	*n* (%)	Deaths (%)
Superficial abscesses	23 (32.9)	9 (39.1)	9 (39.1)	7 (77.8)	14 (60.9)	2 (14.3)
Deep organ abscesses	24 (34.3)	8 (33.3)	8 (33.3)	6 (59.0)	16 (66.7)	2 (12.5)
Pneumonia	18 (25.7)	13 (72.2)	12 (66.7)	10 (83.3)	6 (33.3)	3 (50)
Septic arthritis	15 (21.4)	10 (66.7)	10 (66.7)	8 (80)	5 (33.3)	2 (40)
Neurological disease	7 (10)	3 (42.9)	2 (28.6)	1 (50)	5 (71.4)	2 (40)
Bacteremia	47 (67.1)	32 (68.1)	31 (66)	25 (80.6)	16 (34)	7 (43.8)

*Row percentage. A few patients had multiple presentations

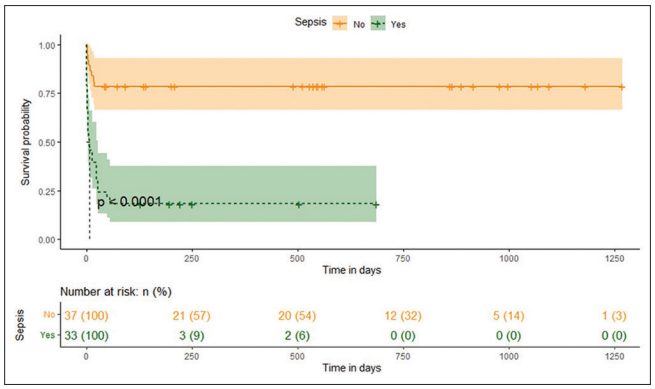

Figure 2: Kaplan–Meier survival plots of patients stratified by sepsis

There were 9 cases of splenic and hepatic abscesses each. The greater frequency of splenic and hepatic abscesses when compared to prostatic abscesses mirrors the scenario in Thailand and Singapore.[18,19] In contrast, Australia reports a higher number of prostatic abscesses.[8] The incidence of genitourinary melioidosis in Indian studies varies from 6.5% to 14% which is similar to the present study (8.6%).[2,4] There were four patients with prostate abscess while renal and tubo-ovarian abscess was documented in one patient each.

Parotitis in children appears to be common in Thailand with one study reporting 38% but was not seen in Australian children.[8,20] The current study included a single case of parotitis involving a 40-year-old female.

Septic arthritis, a well-recognized manifestation of melioidosis, commonly involves joints of the knee and shoulder.[21] Bone and joint involvement in melioidosis range from 7.6% in Australia to 48% cases in Thailand.[22,23] *B. pseudomallei* is the most common cause of septic arthritis with a high (case fatality rate) in Northeast Thailand. An association of *B. pseudomallei* septic arthritis and blood culture positivity with in-hospital mortality was found in Thailand.[23] Similarly, in the present study, 73.3% of septic arthritis patients were bacteremic of whom 8 (72.7%) patients expired during the hospitalization. Patients with both prostate abscess and septic arthritis are likely to have melioidosis.[23] Therefore, in such patients, melioidosis should be considered as a differential diagnosis, in addition to tuberculosis which is prevalent in our region.

Neuromelioidosis accounted for 3% and 5% of cases in Thailand and Australia, respectively[24] while it was encountered in 10% of our patients. Speculation over pathogenesis of neurological melioidosis suggests that it could be due to the direct entry of *B. pseudomallei* to the brain through hematogeneous spread or an exotoxin.[8,25] The clinical and radiologic signs of central nervous system melioidosis can mimic those of neurologic tuberculosis and arboviral encephalitis.[25] Hence, a positive culture report is required to confirm melioidosis and diagnoses should not be made on the basis of clinical signs alone.

The drug of choice for the treatment of melioidosis is meropenem (25 mg/kg up to 1 g) intravenous every 8 h or ceftazidime (50 mg/kg up to 2 g) intravenous every 8 h. This intensive phase is for 14 days. The eradication phase with 3–6 months aims to kill any residual bacteria and minimizes the risk of relapse.[11] In our center, double-strength cotrimoxazole (160 mg trimethoprim - 800 mg sulfamethoxazole) twice a day or doxycycline (100 mg) twice a day alone or in combination are administered during the eradication phase. Although cotrimoxazole is the preferred drug for the eradication phase, doxycycline was used in cases with renal dysfunction or in patients allergic to cotrimoxazole. Of the 70 patients, specific therapy was initiated in 58 (82.9%) patients immediately after isolation of the organism (within 3 days of admission). Not all melioidosis cases necessarily need parenteral therapy. Mild, localized infections can be treated with oral therapy alone.[11] In our study too, a patient with a superficial abscess alone (without sepsis or other clinical manifestations) was treated with double-strength cotrimoxazole twice a day, for 3 months, and fully recovered. However, relapses are not uncommon and the long-term prognosis of these patients who did not receive eradication therapy may be poor.

Relapse has been noted in 3.5% of the patients after 2–7 years even after the eradication phase.[2] In our study, a 45-year-old diabetic farmer with multiple leg abscesses and septic arthritis received complete specific therapy but returned with similar symptoms 6 months after completing therapy. However, due to the existing hospital policy during the ongoing COVID-19 pandemic, the patient could not be admitted. He was discharged on oral antibiotics but expired soon after.

Table 4: Factors associated with mortality in melioidosis patients (*n*=70)

Variables	Nonsurvivors (35%), *n* (%)	Survivors (35%), *n* (%)	Unadjusted		Adjusted	
			HR (95% CI)	*P*	HR (95% CI)	*P*
Age						
≥50 (32)	16 (50.0)	16 (50.0)	0.92 (0.47–1.78)	0.80	-	-
<50 (38)	19 (50.0)	19 (50.0)	1			
Sex						
Male (63)	31 (49.2)	32 (50.8)	0.87 (0.31–2.45)	0.79	-	-
Female (7)	4 (57.1)	3 (42.9)	1			
Diabetes						
Yes (55)	28 (50.9)	27 (49.1)	1.24 (0.54–2.84)	0.61	-	-
No (15)	7 (46.7)	8 (53.3)	1			
CKD						
Yes (9)	8 (88.9)	1 (11.1)	2.14 (0.97–4.73)	0.06	-	-
No (61)	27 (44.3)	34 (55.7)	1			
Alcoholism						
Yes (43)	23 (53.5)	20 (46.5)	1.27 (0.63–2.56)	0.50	-	-
No (27)	12 (44.4)	15 (55.6)	1			
Occupational exposure						
Yes (55)	30 (54.5)	25 (45.5)	1.96 (0.76–5.06)	0.16	-	-
No (15)	5 (33.3)	10 (66.7)	1			
Risk factors†						
Present	32 (49.2)	33 (50.8)	0.81 (0.25–2.64)	0.72	-	-
Absent	3 (60.0)	2 (40.0)	1			
Bacteremia						
Yes (47)	32 (68.1)	15 (31.9)	7.89 (2.41–25.87)	0.001	3.62 (0.96–13.72)	0.06
No (23)	3 (13.0)	20 (87.0)	1			
Sepsis						
Yes (33)	27 (81.8)	6 (18.2)	6.19 (2.79–13.73)	<0.001	3.50 (1.44–8.54)	0.01
No (37)	8 (21.6)	29 (78.4)	1			
Presentation						
Acute (65)	31 (47.7)	34 (52.3)	0.60 (0.21–1.69)	0.33	-	-
Chronic(5)	4 (80.0)	1 (20.0)	1			

†Presence of any one risk factor. HR: Hazard ratio, CI: Confidence interval, CKD: Chronic kidney disease

The risk of death in melioidosis may be influenced by a variety of host factors such as comorbidities and duration of treatment. Risk factors in children with melioidosis are less common and the mortality rate is low, compared to adults.[26] In the present study out of the four children, three survived. The only potential risk factor in them could be environmental exposure to contaminated soil or water. Diabetes mellitus is known to be the single most common risk factor associated with melioidosis due to impaired neutrophil function, as intact neutrophil function and innate immunity play a crucial role against *B. pseudomallei* infection.[1] However, in the present study as well as according to some published reports, diabetes mellitus did not pose an increased risk for death.[2,27]

Other important risk factors include alcohol intake, chronic renal disease, chronic lung disease, malignancy, immunosuppression, and thalassemia.[8] In our study, 61.4% were alcoholics and 12.9% had CKD.

Table 5 shows a comparison of clinical characteristics of melioidosis patients between the present study and previous studies from India. Higher mortality rates are documented in Indian studies 21% to 25.8% compared to other endemic countries.[4,8,19,28] The mortality rate in the present study was 50%. The reason for this high mortality is due to acutely ill bacteremic patients with pneumonia and septic arthritis. Sixty-five (92.9%) patients had acute presentation of which 21 (32.3%) patients presented with symptoms for less than a week. Thirteen (20%) patients died within the first 72 h due to a fulminant septicemic form of melioidosis, in contrast to other Indian studies.

A lower mortality rate of 9.5% was reported by Vidyalakshmi *et al.* from Mangalore.[1] Even though the acute presentation was seen in 71.6% of patients, only 38.9% were bacteremic, in contrast to the present study with 67.1% of bacteremic patients.

The mortality rate reported in a recent study from Puducherry was 25.8% even though they had a much higher proportion of bacteremic cases (90% vs. 67%).[4] However, a direct comparison between the two centers may not be appropriate as in the other study, data on sepsis were not provided.

The strengths of the study are its prospective design with long-term follow-up (ranging from 6 months to 3 years).

Table 5: Comparison with some previous studies from India

Parameter	Present study 2018–2021	Vidyalakshmi *et al*., 2005–2010[1]	Saravu *et al*., 2001–2007[3]	Koshy *et al*., 2008–2014[2]	Basheer *et al*., 2014–2018[4]
Location	Puducherry	Mangalore	Manipal	Vellore	Puducherry
Sample size	70	95	25	114	31
Mean/median age (years)	47.6	50	45	45.6	47.4
Most common risk factor (%)	Diabetes and occupational exposure to soil and water (78.6)	Diabetes (75.8)	Diabetes (68)	Diabetes (81.6)	Diabetes (83.9)
Acute presentation (%)	92.9	71.6	-	36	-
Bacteremic cases (%)	67.1	38.9	36	55.2	90.3
Septicemia/septic shock (%)	47.1	23.2	28	-	-
Most common system/organ involved	Soft tissue	Lung	Liver	Spleen	Soft tissue
Pulmonary melioidosis (%)	25.7	34.7	48	24.5	29
Soft-tissue infection (%)	32.9	11.6	32	13.1	48.4
Neuromelioidosis (%)	10	1.1	4	2.6	12.9
Mortality (%)	50	9.5	8	14.9	25.8

None of the patients were lost to follow-up. However, a low sample size and being a single-centered study are some of the potential limitations. The clinical presentation and risk factors in our population shared overall similarities with other studies from India, with slightly fewer pneumonia cases and more neurological involvement.

Conclusion

In diabetic males and farmers presenting with sepsis, melioidosis should be considered as a differential diagnosis and meropenem should be started as empirical therapy in them with subsequent de-escalation in the absence of laboratory confirmation. Delayed hospitalization among patients with sepsis is associated with high mortality despite initiation of specific therapy.

Research quality and ethics statement

This study was approved by Institutional Ethics Committee) for Human Studies, JIPMER, Puducherry (JIP/IEC/2018/0230). The authors followed the applicable EQUATOR Network (http://www.equator-network.org/) guidelines, specifically the STROBE guidelines, during the conduct of this research project. We also certify that we have not plagiarized the contents in this submission and have done a plagiarism check. We also certify that none of the authors is a member of the Editorial Board of the Journal of Global Infectious Diseases.

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Conflicts of interest

There are no conflicts of interest.

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