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ORIGINAL ARTICLE

Epidemiological and Clinical Features of Talaromycosis (Penicilliosis) Marneffei among Human Immunodeficiency Virus-Infected Patients in Malaysia

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ABSTRAK

Wabak AIDS di Asia Tenggara telah menyebabkan kenaikan insiden talaromikosis (penicilliosis) marneffei. Kajian keratan rentas ini bertujuan untuk menentukan ciri-ciri kliniko-epidemiologi dan peramal akibat talaromikosis. Kami telah mengenalpasti 191 kes talaromikosis marneffei daripada kultur spesimen steril daripada 191 pesakit jangkitan human immunodeficiency virus (HIV). Talaromikosis meningkat daripada 20-25 (2010-2011) kepada 45-50 kes setahun (2012-2014). Talaromikosis merupakan penyakit petunjuk HIV pada 117 (61.3%) pesakit. Insiden talaromikosis sebagai penyakit petunjuk HIV telah menunjukkan peningkatan daripada 10.7 (2010) kepada 26.4 (2014) kes bagi setiap 1000 pesakit baru HIV. Para pesakit berusia antara 19 dan 74 tahun (purata 37.2±9.4 tahun) dan nisbah lelaki kepada wanita adalah 7.7:1. Kaum Melayu (73, 38.2%) dan Cina (70, 36.3%) adalah yang paling ramai. Manifestasi klinikal yang kerap adalah hilang berat badan (85.9%), demam (84.8%) dan batuk (67%), manakala lesi kulit cuma 42.9% kes. Penyakit seiring yang kerap adalah kandidiasis oral (79.6%), tuberkulosis (36.1%) dan jangkitan hepatitis C (20.9%). Kebanyakan pesakit (93.7%) adalah anemik dengan bacaan haemoglobin purata 9.9±2.3 g/dL, 39% terjejas fungsi hati dan 18.8% pula neutropenik. Kiraan sel CD4 median adalah 16 sel/L. Kebanyakan pesakit (70.4%) menerima amphotericin B intravena diikuti oleh itraconazole. Pada 8 bulan perjumpaan susulan, 148 (81.8%) pesakit masih hidup manakala 33 (18.2%) lagi telah meninggal dunia. Penyalahgunaan dadah intravena, jangkitan serentak enkefalitis toxoplasma dan pneumonia Pneumocystis jiroveci telah meramal secara

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berasingan kesudahan kematian dalam kedua-dua analisis regresi logistik univariat dan multivariat.

Kata kunci: AIDS, HIV, Malaysia, marneffei, penicillium, talaromyces

ABSTRACT

The AIDS epidemic in Southeast Asia has led to a marked rise in the incidence of talaromycosis (penicilliosis) marneffei. The aim of this cross-sectional study was to determine the clinico-epidemiological features and outcome predictors of talaromycosis in Malaysia. We identified Talaromycosis marneffei cases from cultures of sterile specimens from 191 human immunodeficiency virus (HIV)-infected patients. Talaromycosis increased from 20-25 (2010-2011) to 45-50 cases per year (2012-2014). Talaromycosis was the HIV-presenting illness in 117 (61.3%) patients. The incidence of talaromycosis as HIV-presenting illness showed an increasing trend from 10.7 (2010) to 26.4 (2014) cases per 1000 new HIV patients. The patients were between 19 and 74 of age (mean 37.2±9.4 years) and the male to female ratio was 7.7:1. Malay (73, 38.2%) and Chinese (70, 36.3%) were the most prevalent ethnic groups. Common clinical manifestations included loss of weight (85.9%), fever (84.8%) and cough (67%), while skin lesions were only present in 42.9% cases. Common concurrent infections were oral candidiasis (79.6%), tuberculosis (36.1%) and hepatitis C infection (20.9%). Most patients (93.7%) were anaemic with mean haemoglobin level of 9.9±2.3 g/dL, 39% had impaired liver function, and 18.8% were neutropaenic. Median CD4 cell count was 16 cells/L. Most patients (70.4%) received intravenous amphotericin B followed by itraconazole. At 8-month follow up, 148 (81.8%) patients were alive while 33 (18.2%) had died. Intravenous drug abuse, concurrent toxoplasma encephalitis and concurrent *Pneumocystis jiroveci* pneumonia independently predicted death outcome in both univariate and multivariate logistic regression analyses.

Keywords: AIDS, HIV, Malaysia, marneffei, penicillium, talaromyces

INTRODUCTION

Talaromyces (Penicillium) marneffei is a dimorphic fungus that causes a lethal fungal infection known as talaromycosis (penicilliosis) marneffei. Talaromycosis marneffei is endemic especially among human immunodeficiency virus (HIV)-infected patients in Southeast Asia (Vanittanakom et al. 2006; Le et al. 2011; Nor-Hayati et al. 2012; Drouhet 1993). Cases were also reported in other countries but patients often had a travel history to the endemic region of *T. marneffei* (Sirisanthana & Supparatpinyo 1998). Talaromycosis marneffei is an important HIV-associated opportunistic infection in South and Southeast Asia, ranking third after tuberculosis and cryptococcal

meningitis (Supparatpinyo et al. 1994). In Thailand, the prevalence among HIV infected patients was about 60% (Sirisanthana & Supparatpinyo 1998). In Vietnam, talaromycosis mean incidence of 4.4% was directly proportionate to the trends of AIDS admissions between 2004 and 2009 (Le et al. 2011). Talaromycosis in Malaysia has not been extensively studied. A previous study in Malaysia reported that the prevalence of *T. marneffei* among all fungi cultured from clinical specimens was 14% (Tzar et al. 2013). In view of a growing HIV incidence in Malaysia, we conducted a larger scale study to determine the epidemiology, clinical features and outcome predictors of Talaromycosis marneffei among HIV-infected patients in Malaysia. This study may give the latest information about the disease burden, trend and clinical features of Talaromycosis marneffei in Malaysia. In addition, clinicians may be able to prognosticate the outcome of the patients based on significant variables found in this study.

MATERIALS AND METHODS

A retrospective, cross sectional study was conducted at Hospital Sungai Buloh (an infectious disease reference centre in Malaysia) from January 2010 to December 2014. By using a formula by Kish (1965), the calculated sample size was 185 cases. Cultures of specimens, which are positive for *T. marneffei* were identified from the hospital laboratory (eHIS data statistic) system. Only normally sterile specimens were included in this study such as blood, cerebrospinal fluid, bone marrow, tissue and bronchoalveolar lavage. Patients with multiple positive cultures from different specimens were counted only once. Duplicate results and specimens referred from other institutions were excluded. Patient demographic data such as age, sex and race and information regarding clinical presentation, concurrent infections, risk factors, laboratory values (CD4 count, liver function tests, haemoglobin level, and neutrophil count) and patients' outcome were obtained from the eHIS system. Clinical outcomes were assessed at 8 months after discharge. Clinical outcomes were categorized as alive, deceased or non-assessable. Non-assessable data (such as transfer out to other hospital or follow-up in other health-care centre or defaulted clinic appointment) were treated as missing data when analysing the outcome. Data were analysed by the Statistical Program for Social Sciences (SPSS) version 17. Regression tests were used to compare clinical and laboratory characteristics, with $p<0.05$ was taken to indicate statistical significance.

RESULTS

In 5 years study period (2010 until 2014), 418 specimens were positive for *T. marneffei*. However, 227 of 418 specimens were excluded: 188 specimens were duplicates from the same patients; 37 specimens were referred from external healthcare centres; and two cases were excluded on suspicion of contamination. The first of the two presented with a fungating verrucous mass on the dorsum of the

Table 1: Demographics of cases of talaromycosis marneffei (n=191)

Characteristics	n (%)
Male (male to female ratio = 7.7:1)	169 (88.5)
Mean age in years ± SD (range)	37.15 ± 9.38 (19-74)
Malay	73 (38.2)
Chinese	70 (36.3)
Indian	25 (13)
Other races	23 (11.9)

third toe, which was diagnosed as squamous cell carcinoma on biopsy. The second patient presented with an open fracture of femur and tibia due to motor vehicle accident and developed fever on day nine of admission with a positive blood culture for *T. marneffei.* However, both patients showed no clinical signs and symptoms of talaromycosis, hence the clinicians regarded the isolates as contaminant and did not start the patients on any antifungal medication. Thus, only 191 cases were included in this study. Out of 191 patients, 183 (95.8%) had positive cultures for *T. marneffei* from blood while the remaining was from tissues. Bone marrow, body fluids and cerebrospinal fluids yielded no positive cultures. Male to female ratio was 7.7:1. They were all adults with a mean age of 37.15±9.38 years (range 19-74 years). Malay and Chinese patients formed about three-quarter of all cases. Other races included 14 Burmese, six Indonesians, one Sabahan Bumiputera, one Thai and one Libyan (Table 1).

All 191 patients in this study were HIV seropositive, with 117 (61.3%) of them were newly diagnosed HIV on further investigations following positive cultures for *Talaromyces marneffei* (Table 2). From 2010 to 2014, the number of new cases of talaromycosis increased from 26 to 49 per year. In addition, the incidence of talaromycosis as an HIV-presenting illness also increased every year from 10.7 talaromycosis per 1000 new HIV patients in 2010 to 30.84 in 2013, with

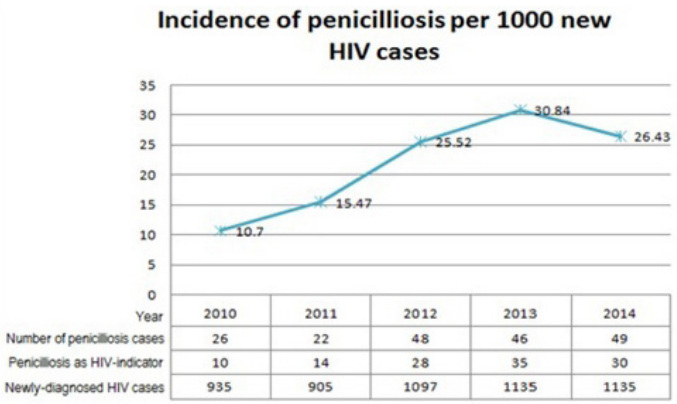

Figure 1: Talaromycosis (penicillosis) incidence per 1000 new HIV patients from 2010-2014

Table 2: Clinical features of patients with talaromycosis marneffei (n=191)

Clinical characteristics	n (%)
Clinical manifestations	
Weight loss	164 (85.9)
Fever	162 (84.8)
Cough	128 (67.0)
Skin lesion	82 (42.9)
Lymphadenopathy	81 (42.4)
Hepatomegaly	80 (41.9)
Diarrhoea	74 (38.7)
Splenomegaly	12 (6.3)
Concurrent infections	
AIDS/HIV infection	191 (100)
Oral candidiasis	152 (79.6)
Tuberculosis	69 (36.1)
Hepatitis C	40 (20.9)
Pneumocystis jiroveci pneumonia	28 (14.7)
Syphilis	16 (8.4)
Hepatitis B	15 (7.9)
Salmonellosis	12 (6.3)
Toxoplasma encephalitis	8 (4.2)
Cytomegalovirus infection	7 (3.7)
Herpes infection	7 (3.7)
Histoplasmosis	3 (1.6)
Cryptococcosis	2 (1.0)
Rhodococcosis	1 (0.5)
Leishmaniasis	1 (0.5)
HIV status	
Newly diagnosed HIV infection	117 (61.3)
Known HIV-infected patients	74 (38.7)
Antiretroviral-defaulted	43 (58.1)
Antiretroviral-naïve	26 (35.1)
Antiretroviral just started on presentation	5 (6.8)

a slight reduction to 26.43 in 2014 (Figure 1).

Weight loss, fever and cough were the three most common clinical manifestations, present in more than half of the patients. Meanwhile, skin lesions, lymphadenopathy, hepatomegaly and diarrhoea were present in about 40% of the cases. All of them were HIV-infected patients and 61.3% were newly diagnosed with HIV infection. Most of the known HIV-infected patients have defaulted their antiretroviral therapy. Other concurrent

Table 3: Laboratory characteristics of patients with talaromycosis marneffei (n=191)

Laboratory characteristics	Median[a] /Mean[b] Value	n (%)
CD4 cell count, cells/µl (n =187)	16 (7, 35)[a]	
50 cells/µL		155 (82.9)
51-100 cells/µL		26 (13.9)
101-200 cells/µL		6 (3.2)
Neutrophil counts, (x 10^9/L)	3.34 (2.36, 4.68)[a]	
Neutropaenic (<2 x 10^9/L)		36 (18.8)
Not neutropaenic (≥2 x 10^9/L)		155 (81.2)
Haemoglobin (g/dL)	9.9 ± 2.3 (1.3-16.4)[b]	
Anaemic (<11.5g/dL female, <13.5g/dL male)		179 (93.7)
Not anaemic (≥11.5g/dL female, ≥13.5g/dL male)		12 (6.3)
Alanine aminotransferase, ALT (U/L)	38 (22, 77)[a]	
High (>55U/L)		75 (39.3)
Normal (≤55U/L)		116 (60.7)
Alkaline phosphatase, ALP (U/L)	122 (74, 214)[a]	
High (>150U/L)		74 (38.7)
Normal (≤150U/L)		117 (61.3)

[a]median (25th percentile, 75th percentile), [b]mean ± standard deviation (range)

infection included oral candidiasis (79.6%), tuberculosis (36.1%), hepatitis C (20.9%), PCP (14.7%), syphilis (8.4%) and hepatitis B (7.9%) (Table 2).

In this study, 82.9% had very low CD4 cell counts. The median CD4 count was 16 cells/L. However, 81.2% were not neutropaenic. The median neutrophil count was 3.34x10^9/L, which was well within the reference range. Majority of the patients (93.7%) were anaemic, with a mean haemoglobin count of 9.9±2.3 g/dL and more than 60% did not show elevated liver enzymes, with median ALT and ALP counts of 38U/L and 122U/L, respectively (Table 3).

Antifungal treatment was initiated in 169 (87.6%) of 191 patients. Of 169 patients, 147 (87%) were treated with intravenous amphotericin B deoxycholate as induction therapy followed by itraconazole (119 patients, 70.4%) or fluconazole (28 patients, 16.6%) as maintenance therapy. The standard therapy consisted of intravenous amphotericin B deoxycholate 0.6-0.7 mg/kg/day for 2 weeks, followed by oral itraconazole 400 mg/day for 8 to 10 weeks. After completion of treatment, all patients received oral itraconazole 200 mg/day as a secondary prophylaxis until the CD4 level is above 200 cells/µL. Other patients received antifungal monotherapy, either with itraconazole (8 patients, 4.7%), fluconazole (3 patients, 1.8%) or amphotericin B (11 patients, 6.5%). These patients were not admitted because of mild symptoms, admission refusal, being transferred to other hospital or patients who passed away during induction therapy with amphotericin B (Table 4).

Table 4: Treatment, outcome and CD4 counts of talaromycosis marneffei patients

Variables	n (%)
Treatment received (n = 169)	
Amphotericin B then itraconazole	119 (70.4)
Amphotericin B then fluconazole	28 (16.6)
Itraconazole	8 (4.7)
Fluconazole	3 (1.8)
Amphotericin B	11 (6.5)
Outcome (n = 181)	
Alive	148 (81.8)
Deceased	33 (18.2)
CD^4 cell count before therapy (n = 187)	16 (7, 35)[a] cells/μL
CD^4 cell count after therapy (n = 137)	169 (110,228)[a] cells/μL

[a]median (25^{th} percentile, 75^{th} percentile)

The outcome was only known for 181 patients. The remaining 10 patients were transferred to other healthcare centres for follow-up care. Of the 181 patients, 148 (81.8%) patients were alive at 8-month assessment after discharge. All-cause mortality rate among the patients was 18.2% (33 out of 181 patients). The causes of death included nosocomial sepsis (8), talaromycosis or severe fungaemia (7), severe sepsis including rhodococcal sepsis (6), disseminated tuberculosis and tuberculous meningitis (3), upper gastrointestinal bleeding (3), meningoencephalitis and encephalitis (3), severe *Pneumocystis jiroveci* pneumonia (2) and haemophagocytosis (1). The median CD4 cell count at four months to one year after therapy was 169 cells/μL as compared to 16 cells/μL prior to therapy (Table 4).

All covariates were analyzed using univariate logistic regression analysis to assess the prediction of outcome. All non-missing covariates and outcomes were assessable in 181 patients (94.7%). Univariate logistic regression analysis showed that median age, diarrhoea, P*neumocystis jiroveci* pneumonia (PCP), toxoplasma encephalitis, intravenous drug user (IVDU) and high alkaline phosphatase (ALP) were significant predictors of patient outcome. However, in multivariate logistic regression analysis, only concurrent PCP (adjusted odds ratio [AOR], 9.892; 95% CI, 3.1-31.1; P<0.001), concurrent toxoplasma encephalitis (AOR, 7.509; 95% CI, 1.2-44.0; P=0.025) and IVDU (AOR, 5.462; 95% CI, 1.7-17.1; P=0.004) showed to be significant independent predictors of outcome (Table 5).

DISCUSSION

Talaromyces marneffei infection in HIV patients was first reported in Malaysia in 1995 (Rokiah et al. 1995). A previous study in Hospital Kuala Lumpur Malaysia reported seven cases of talaromycosis among 419 HIV/AIDS patients (1.7%) between 1994 and 2001 (Nissapatorn et al. 2003). Subsequently in 2012, a

Table 5: Analyses of risk factors and association with death outcome in 181 patients with talaromycosis marneffei

Variables	Alive n=148 (%)	Deceased n=33 (%)	Univariate analysis			Multivariate analysis		
			Crude OR	95% CI	p value	Adj OR	95% CI	p value
Median age (IQR)	35 (29,41.5)	37 (33,49)	1.05	(1.01,1.09)	0.0011	1.044	(0.9,1.1)	0.087
Diarrhoea	52 (35.1)	18 (54.5)	2.215	(1.0,4.7)	0.041	1.475	(0.5,4.0)	0.45
PCP	13 (8.8)	14 (42.4)	7.625	(3.1,18.7)	<0.001	9.892	(3.1,31.1)	<0.001
Toxoplasma encephalitis	4 (2.7)	4 (12.1)	4.966	(1.1,21.0)	0.029	7.509	(1.2,44.0)	0.025
IVDU	16/138 (11.6)	9/28 (32.1)	3.67	(1.2,7.8)	0.0017	5.462	(1.7,17.1)	0.004
High ALP	51 (34.5)	18 (54.5)	2.282	(1.0,4.0)	0.034	0.692	(0.2,1.8)	0.461

IVDU: intravenous drug user; PCP: Pneumocystis jiroveci pneumonia, OR: odds ratio, ALP: alkaline phosphatase

retrospective review on characteristics of twenty advanced HIV patients with *Talaromyces marneffei* infection was published (Nor-Hayati et al. 2012). Our study is the largest talaromycosis case review in Malaysia on clinical and epidemiological data, and we report for the first time, the burden of and the predictors of outcome of talaromycosis in Malaysia with mean incidence of 21.79 cases per 1000 newly diagnosed HIV patients. Both talaromycosis and newly diagnosed HIV trends reflect the HIV/AIDS epidemic in Malaysia.

Male, Malays and Chinese were the most prevalent gender and races who presented with Talaromycosis marneffei in this study. Male is known to be a predominant gender ranging from 70-80% in other studies of talaromycosis (Kawila et al. 2013; Le et al. 2011; Nor-Hayati et al. 2012). Previous studies in Northern Thailand and Vietnam had shown that cases of talaromycosis among HIV-infected patients were younger (between 28 and 48.5 years) than HIV uninfected patients (between 50 and 64 years) in (Kawila et al. 2013; Le et al. 2011). Our study among HIV-infected patients showed a wider age spread between 19 and 74 years (mean age 37.15±9.38 years), which is similar to a previous study in Malaysia by Nor-Hayati et.al. (2012). The reason for this variation is unclear.

Common clinical presentations of Talaromycosis marneffei in this study were loss of weight, followed by fever, cough, skin lesion, lymphadenopathy, hepatomegaly, diarrhoea and splenomegaly. In Vietnam and Thailand, fever is a more common clinical presentation followed by loss of weight, skin lesion, cough and hepatomegaly (Le et al. 2011; Kawila et al 2013). However, some symptoms like loss of weight and fever are neither specific nor diagnostic for talaromycosis as they could also be associated with late HIV infection. Since all patients in this study were HIV-infected, it is not surprising that most concurrent infections were the usual opportunistic infections seen in AIDS patients. We found oral candidiasis, tuberculosis,

hepatitis C infection and *Pneumocystis jiroveci* pneumonia (PCP) as the most common concurrent infections. Similar trends of concurrent infections were also reported in Vietnam but at lower percentages, oral candidiasis (49%), tuberculosis (22%) and PCP (4%) (Le et al. 2011).

HIV-infected talaromycosis patients were more likely to be leukopaenic than non-HIV-infected patients (Li et al 2016; Kawila et al. 2013). Correspondingly, we found that the median CD4 count was low at 16 cells/μL, which was similar to other studies that ranged from 7 cells/μL to 14 cells/μL (Le et al. 2011; Nor-Hayati et al. 2012; Kawila et al 2013). Nearly all cases (96.8%) had CD4 counts of less than 100 cells/μL and 82.9% less than 50 cells/μL, which were a little bit higher compared to another study in Thailand (91.7% and 71.2% of cases, respectively) (Chariyalertsak et al. 1997). Anaemia was seen in 93.7% of patients with a mean haemoglobin level of 9.9±2.3 g/dL (1.3 g/dL-16.4 g/dL). Anaemia is a common manifestation of talaromycosis as being reported elsewhere (Le et al. 2011; Kawila et al 2013). About 39% of our infected patients had elevated ALT and ALP levels but in general, the median values fell within normal limits (38U/L and 122U/L, respectively). However, a previous study in the same setting showed an elevated median ALP (259U/L) but normal median ALT (48U/L) (Nor-Hayati et al. 2012) while a study in Vietnam showed slightly elevated mean ALT level of 60U/L (Le at al. 2011). Nevertheless, the variations in the liver enzyme levels could not be directly attributed to talaromycosis because there are many factors that could contribute to this such as concurrent viral hepatitis and drugs.

Talaromycosis is frequently reported as a late manifestation of HIV infection (Supparatpinyo et al. 1992; Hung et al. 1998; Le et al. 2011; Kurup et al. 1999; Ranjana et al. 2002). We found that almost two-thirds (61.3%) of our patients presented with talaromycosis as an HIV presenting illness (newly diagnosed HIV), which is about 2.5 times higher than a study in Vietnam involving 513 patients (Le et al. 2011). These findings together with median CD4 of 16 cells/μL may support the idea of listing talaromycosis as an HIV/AIDS-indicator disease in Malaysia just like in Hong Kong and Thailand (Imwidthaya 1994; Wong et al. 1995). The study in Vietnam reported that predictors of poor outcome of talaromycosis included IVDU, shorter history, absence of fever or skin lesions, higher respiratory rates, higher absolute lymphocyte count and lower platelet count (Le et al. 2011). However, we found that only IVDU, concurrent toxoplasma encephalitis and concurrent PCP independently predicted death outcome. These outcome predictors may help clinicians to prognosticate the disease outcome. PCP and toxoplasma encephalitis are AIDS indicator diseases when the CD4 count is less than 200 cells/μL, while IVDU is an established independent risk factor for death and/or development of AIDS (Gadpayle et al. 2012). Because HIV infection or AIDS is a known risk factor for

Talaromycosis marneffei, IVDU is indirectly related to talaromycosis. Since all patients in this study were HIV positive, we tried to explore whether the mode of HIV acquisition has any weight on the outcome of patients infected with *Talaromyces marneffei*. Apparently, IVDU shows significant association to death but not the other modes of acquisition. The reason for this is unclear. Perhaps patients with IVDU had more severe HIV infection and subsequently more severe talaromycosis, which led to higher rates of death. Further, more detailed studies are needed to elucidate this, possibly even at molecular levels. Absence of fever or presence of skin lesions was not found to be a significant predictor even during univariate analysis. The laboratory characteristics such as neutrophil count, haemoglobin, ALP, ALT and CD4 levels were also not significant predictors of mortality. The mortality rate of talaromycosis in this study was 18.2%, which is a bit lower than 20-29% mortality rates in Vietnam and Thailand (Le at al 2011; Kawila et al. 2013). Most of our patients who recovered from talaromycosis received the recommended treatment for talaromycosis, which is intravenous amphotericin B as an induction therapy followed by oral itraconazole as a maintenance therapy (Ministry of Health Malaysia 2014). Our study limitations include a relatively small sample size, retrospective study design with some missing data and absence of autopsy evidence to the causes of deaths. However, despite these limitations, this study still provides the latest and largest clinico-epidemiological data and outcome predictors of talaromycosis in Malaysia. In conclusion, Talaromycosis marneffei incidence in Malaysia is rising among HIV infected patients. The most common clinical manifestations are loss of weight, fever and cough. Concurrent IVDU, toxoplasma encephalitis and PCP were significantly associated with mortality.

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