Texila International Journal of Academic Research
ISSN: 2520-3088
DOI: 10.21522/TIJAR.2014.10.04.Art008

Association between Prevalence of Talaromycosis and Economic Status in Asia

Thanh Nguyen Tat[1,2]*, Dat Nguyen Tat[1], Praveen T. Krishnamurthy[3]
[1]*Medical Doctor, School of Clinical Research, Texila American University, Guyana*
[2]*Woolcock Institute of Medical Research, Ho Chi Minh City, Vietnam*
[3]*Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education and Research, The Nilgiris, Ooty – 643001*

Abstract

Previous studies have shown that geographic niche was a significant risk factor for developing T. marneffei (Tm) infection, and to date there are still lacking data of impact of economic status on the prevalence of Tm. Thus, we conducted this study, aiming to examine the correlation between prevalence of talaromycosis among HIV/AIDS-infected adult population and Asian country income, reported by World Bank data. A comprehensive medical literature review was performed to estimate the prevalence of T. marneffei infection among HIV/AIDS-infected adult population in Tm endemic and non-endemic countries and country income in Asia. Linear regression analyses were used to study the associations between Tm prevalence and Asian country income. Both unadjusted and adjusted models with Tm geographic distribution were analysed. A total of 48 Asian countries were included in the statistical analysis. Geographic distribution of talaromycosis was divided into three main regions: (i) Region 1: Regions of highest incidence of talaromycosis (>100 Tm cases reported in literature); (ii) Region 2: Endemic Tm countries and (iii) Region 3: Countries of imported or travel-associated Tm cases. Estimated Tm prevalence in the three regions were 3.9%, 2% and 0.02%, respectively. There was no statistical difference in GDP among three regions (P = 0.70). The linear regression analyses showed no associations between prevalence estimates of talaromycosis and Asian country income in both unadjusted and adjusted for geographic distribution of T. marneffei (P = 0.83). Most markedly, country geography is still a significant risk factor for T. marneffei infection *(P < 0.001).*

Keywords: *Economic status, Invasive fungal infections, Prevalence, Talaromyces marneffei, Vietnam.*

Introduction

Talaromyces marneffei (Tm) is a dimorphic fungus that can cause a life-threatening systemic infection in immunocompromised individuals living in or traveling to Southeast Asia and southern China [1, 2]. The Tm mortality on antifungal therapy ranges from roughly 10% to 30% [3-8]. Talaromycosis has been mainly reported in the Southeast Asia (particularly Thailand and Vietnam), southern China, Hong Kong, and Eastern India [3, 9]. Geographic distribution of talatomycosis has been increasingly reported [3, 9, 10]. The ecosystems including climatic conditions in the endemic regions can facilitate the growth of *T. marneffei*, combined with high humidity are important risk factors to expand the fungal reservoir in the environment and to enhance the fungal infection through air-borne transmission [3]. Recently, Narayanasamy et al. assumed an association between talaromycosis and poverty in Asia, based on mapping distribution of *T.*

Received: 17.08.2023 ***Accepted: 05.09.2023*** ***Published on: 30.10.2023***
****Corresponding Author: thanhntoucru@gmail.com***

marneffei in correlation with Asian country income [10].

Most markedly, geographic restriction of talaromycosis in Asian countries in tropical and subtropical regions mostly falls in low and lower middle-income nations in which the Gross National Incomes per capita (or GDP) range from USD $ 1,036 to $ 4,045 annually, reported by the World Bank data [11]. Up to two-thirds of inhabitants in talaromycosis hyperendemic regions are living in poor rural areas, for instance 63% of the Vietnamese, 67% southern China provinces and 50% Thai population [10, 11]. On this basis, our primary study hypothesis was that low and low-middle-income countries had higher prevalence of talaromycosis than upper-middle-income and high-income countries, and there may be an association between Tm prevalence and economic status in Asian countries. Therefore, we conducted this study, aiming to investigate the possible association between prevalence of *T. marneffei* and economic status of countries in Asia, as defined by country income (GDP).

Materials and Methods

Ethics Statement

We used the secondary datasets from World Bank data from 2021 report [11] and from medical literature review for Tm prevalence estimates [12-21]. The study datasets were publicly available for accessibility. Using secondary dataset was causing less than minimal risk to study participants, in this respect the ethical clearance for this study was suggested to be waived off.

Study Setting, Design and Population

All Asian countries were included in the analysis to study the association between country incomes, reported by World Bank data report in 2021 [11], and talaromycosis prevalence estimates, based on available published data [12-21]. Geographic distribution of talaromycosis has three main regions [3, 9, 10]:

1. **Region 1**: ***Regions of highest incidence of talaromycosis*** (> 100 reported cases), including: China, Thailand and Vietnam.
2. **Region 2**: ***Endemic Tm countries***, including: Cambodia, Laos, Brunei, Myanmar, Indonesia, Malaysia, Singapore, Philippine, Hong Kong, Taiwan and India.
3. **Region 3**: ***Regions of imported or travel-associated cases,*** including: Japan, South and North Korea, Afghanistan, Yemen, Syria, Tajikistan, Bangladesh, Bhutan, Comoros, Kyrgyz Republic, Mongolia, Nepal, Pakistan, Timor-Leste, Uzbekistan, Armenia, Iran, Iraq, Jordan, Lebanon, Maldives, Turkmenistan, Saudi Arabia, United Arab Emirates, Israel, Oman, Kuwait, Qatar, Bahrain, Macau, British Virgin Islands, Palestine, Azerbaijan, Georgia.

Data Collection

We performed a comprehensive medical literature review to calculate estimates for *T. marneffei* prevalence (%) in HIV-infected population and Asian country income (in GDP per capita) retrieved from World Bank data (2021 report).

Study Assumption for Estimates of Tm Prevalence in Non-endemic Region

Due to the limited data of *T. marneffei* in non-endemic countries in Asia [16-21], assumptions were reasonably raised and used for the statistical analysis:

1. Neighbouring countries, sharing the similar geographic and climatic conditions would have the similar risk of Tm development.
2. Countries with unavailable data of Tm prevalence will be imputed the median Tm prevalence estimate of the whole areas (either regions 1, 2, or 3 as defined above).

For example, Oman is located in the middle east of Asia and classified as non-endemic Tm region reported with 02 incident Tm cases travelling to Southeast Asia among 10,000 HIV-infected people in the country [16]. Thus,

neighbouring countries juxtaposed with Oman such as, Yemen, Yemen, Syria, Iran, Iraq…etc, with unavailable Tm prevalence data would be assumed to have similar risk of Tm development as Oman and would share the median Tm prevalence estimate of the whole non-endemic region [16, 17].

Statistical Analysis

Summary statistics are either median (interquartile), or mean and standard deviation (± SD) for continuous variables and percentage (%) for categorical variables. The Fisher exact test was used to compare two proportions, and ANOVA tests with post-hoc Tukey pairwise comparisons were used for 03 group comparisons of continuous variables. Linear regression analysis was used to study the associations between Tm prevalence and Asian country income. Both unadjusted and adjusted models with geographic distribution of talaromycosis were analysed for associations, on the basis that geographic distribution in the defined regions is a significant factor for *T. marneffei* infection, as demonstrated in previous studies [3, 9, 10, 15]. Significance level was set at $P < 0.05$ for all analyses. R software was used for all statistical analysed.

Results

Tm Prevalence Estimates

Overall, the median estimated Tm prevalence was 2 % (95 % credibility interval: 0.02 % to 3.2 %), with the highest Tm burden in Vietnam, Thailand, and southern China with Tm prevalence, hovering around 4% among HIV/AIDS patients [6-9, 12-15]. Table 1 shows the estimates and 95% credibility interval of estimated Tm prevalence, categorized by levels of Tm endemic. The highest Tm density including Vietnam, Thailand and southern China had the median Tm prevalence of 3.9% (95% credibility interval: 3.3% – 6.4%) among people living with HIV/AIDS. The Tm prevalence in endemic regions had a median of 2%, while that of non-endemic Tm regions was estimated approximately 02 Tm cases among 10,000 HIV/AIDS patients. Most markedly, there were statistical differences in Tm prevalence in these three defined regions, with *P* value < 0.001 (Fisher exact test).

Table 1. Estimates of Tm Prevalence among Adult HIV/AIDS Population in Asian Countries

Tm Regions	**Tm prevalence estimates (%)**	***P*-value ***
Regions of highest Tm incidence	3.9 (3.3-6.4)	< 0.001
Endemic region	2 (2-2.1)	
Regions of disease imported or travel-associated areas	0.02 **	

Notes. Summary statistic is median of estimates and 95% credibility of interval. * P value withdrawn from Fisher exact test, ** 02 Tm incident cases among 10,000 HIV-infected people

Asian Country Incomes, Reported from World Bank 2021 Report

Table 2 presents incomes of Asian countries, categorized by Tm endemic. Markedly, there was no statistical difference in country income by GDP per capita (in USD), in three main regions of Tm endemic ($P = 0.70$). The further pairwise comparisons also revealed no differences in nation income among three Tm regions.

Table 2. Comparisons of Country Gross Domestic Product Per Capita (GDP) (in USD $) in Asian Countries by Endemic Regions of Talaromycosis

Tm endemic regions	**Mean**	**SD**	***P*-value ***
Region 1-Hyperendemic Tm regions	6,803	3,839	0.70
Region 2-Endemic Tm regions	15,872	21,357	
Region 3-Non-endemic regions or countries reported with travel-related Tm cases	12,552	15,647	
Pairwise comparisons between groups: income difference and *P* values **:			
Regions 1 and 2: Difference = 9,069 (USD), *P* = 0.96			
Regions 2 and 3: Difference = 3,320 (USD), *P* = 0.85			
Regions 1 and 3: Difference = 5,749 (USD), *P* = 0.84			

Statistics are means and standard deviation (± SD) for the parameter-GDP; * P-value withdrawn from ANOVA test for all three-group comparison; ** P-values from Tukey tests for pairwise comparisons between groups

Associations between Tm Prevalence and Economic Status (in GDP) in Asian Countries

As shown in Table 3, there were no associations between Tm prevalence and economic data in term of country GDP per capita in Asian countries from both unadjusted and adjusted linear regression analyses. Notably, in the adjusted linear regression, geographic distribution of *T. marneffei* was significantly associated with Tm prevalence.

In addition, Figure 1 represents the fitted line (bold blue line) for the association between Tm prevalence and Asian country GDP (USD). The fitted line was quite flat, indicating insignificant correlation between these two variables. The further analysis of model residual, showing the non-normality distribution as shown in Figure 2. This is mainly due to the limited data of Tm prevalence included in study analysis.

Table 3. Associations between Economic Status Demonstrated by Country Income in GDP Per Capita and Estimates of Prevalence of Talaromycosis in Asian Countries

Unadjusted linear regression analysis			
Coefficient	Estimate	SE	*P*-value*
Country income	0.00000588	0.00014	0.97
Adjusted linear regression analysis by geographic of Tm			
Coefficients	Estimates	SE	*P*-value**
Country income	0.00000898	0.00042	0.83
Tm geographic distribution (Reference = Region 1)			
Region 2 vs Region 1	-0.0281	0.003	<0.0001
Region 3 vs Region 1	-0.0451	0.0027	<0.0001

Statistics are estimates of coefficients and standard errors (SE); * P value withdrawn from unadjusted model; ** P value withdrawn from adjusted model with geographic distribution of talaromycosis

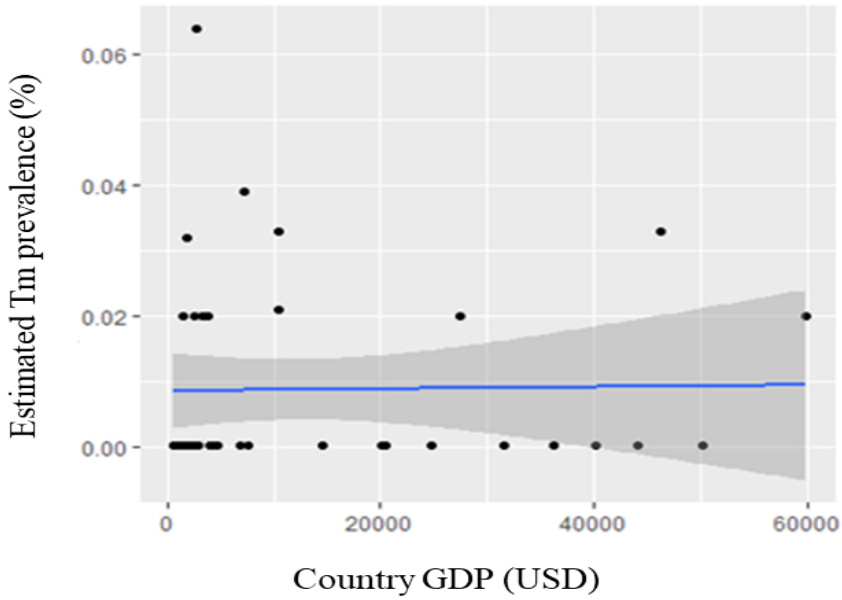

Figure 1. The Correlation between National GDP Per Capita and the Talaromycosis Prevalence Estimates in Asian Countries

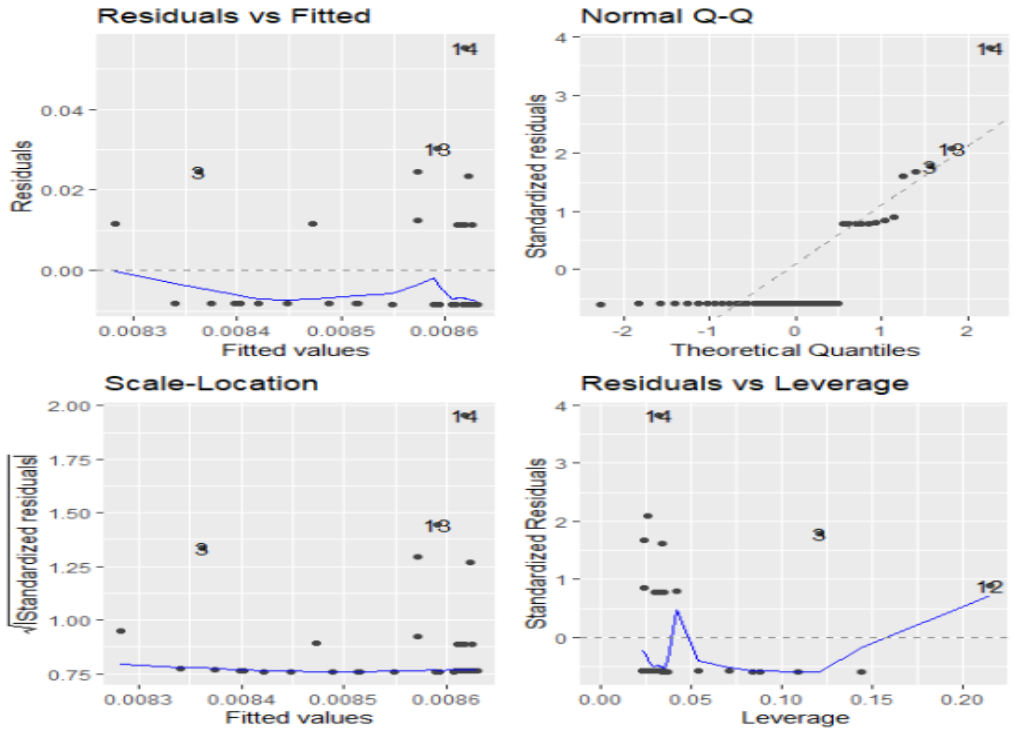

Figure 2. The Non-normality of Residual from Adjusted Linear Regression Model

Discussion

The findings from this study were quite consistent with previously published data about prevalence of *T. marneffei* infection among HIV/AIDS population [15]. Talaromycosis has remained a major burden among HIV populations in Asian countries [9, 15]. There has been a marked variation in Tm prevalence associated with geographic regions and countries in Asia. This study continued to firmly show the significant association between geographic areas and the prevalence of talaromycosis in Asian regions ($P < 0.0001$). Although Narayanasamy supported the correlation between frequency of talaromycosis

and economic status of countries enduring the Tm endemic in Asian regions [10], our study revealed no statistical association between Tm prevalence and economic status in both unadjusted and adjusted linear regression analyses. However, this study finding should be carefully interpreted because of limited data about Tm prevalence in non-endemic regions and non-normality of residual parameter from modelling. Markedly, our study finding is consistent with results reported from a systematic review and meta-analysis conducted by Qin Y et al. in 2020 that there was no statistical association between Tm prevalence and country income with odds ratios (OR) = 0.466 (95% CI: 0.771 to 2.831, P = 0.393, from the meta-regression analysis) [15]. On this basis, I support that geographic distribution of regions in defined Asian countries through favourable ecosystems and climatic conditions including humidity, temperature and particular in rainy seasons is still the most significant risk factor for *T. marneffei* infection and air-borne transmission [3]. Economic status has no association with the frequency of talaromycosis in Asian regions.

Our study has several limitations. Firstly, using secondary datasets to perform a post-hoc analysis is considered a primary limitation. Secondly, there were limited data about prevalence of talaromycosis reported in non-endemic regions so that the study lacks sufficient power to draw a robust conclusion.

Conclusion

This study showed no correlation between economic status, in term of country GDP per capita and the prevalence of talaromycosis in Asian countries. In addition, our study finding strengthens the impact of geography on the development of talaromycosis.

Conflicts of Interest

All authors declare no conflict of interest.

Financial Support and Sponsorship

The study was self-funded.

Acknowledgements

We thank publicly accessed data sources for the analysis in this study.

References

[1] Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated *Penicillium marneffei* infection in southeast Asia. Lancet 1994; 344:110-3.

[2] Vanittanakom N, Cooper CR Jr, Fisher MC, Sirisanthana T. *Penicillium marneffei* infection and recent advances in the epidemiology and molecular biology aspects. Clin Microbio Rev. 2006; 19:95-110.

[3] Le T, Wolbers M, Chi NH, Quang VM, Chinh NT, Lan NP, et al. Epidemiology, Seasonality, and Predictors of Outcome of AIDS-Associated *Penicillium marneffei* Infection in Ho Chi Minh City, Viet Nam. Clin Infect Dis. 2011; 52:945–952.

[4] Larsson M, Nguyen LH, Wertheim HF, Dao TT, Taylor W, Horby P, et al. Clinical characteristics, and outcome of Penicillium marneffei infection among HIV-infected patients in northern Vietnam. AIDS Res Ther. 2012; 9:24.

[5] Son VT, Khue PM, Strobel M. Penicilliosis and AIDS in Hai Phong, Vietnam: Evolution and predictive factors of death. Med Mal Infect. 2014; 44:495-501.

[6] Kawila R, Chaiwarith R, Supparatpinyo K. Clinical and laboratory characteristics of penicilliosis marneffei among patients with and without HIV infection in Northern Thailand: a retrospective study. BMC Infect Dis. 2013; 13:464.

[7] Hu Y, Zhang J, Li X, Yang Y, Zhang Y, Ma J, et al. *Penicillium marneffei* infection: an emerging disease in mainland China. Mycopathologia. 2013; 175:57-67.

[8] Le T, Kinh NV, Cuc NTK, Tung NLN, Lam NT, Thuy PTT, et al. A Trial of Itraconazole or

Amphotericin B for HIV-Associated Talaromycosis. N Engl J Med. 2017; 376:2329-2340.

[9] Cao C, Xi L, Chaturvedi V. Talaromycosis (Penicilliosis) Due to Talaromyces (Penicillium) marneffei: Insights into the Clinical Trends of a Major Fungal Disease 60 Years After the Discovery of the Pathogen. Mycopathologia. 2019; 184:709-720.

[10] Narayanasamy S, Dat VQ, Thanh NT, Ly VT, Chan JF, Yuen KY, et al. A global call for talaromycosis to be recognised as a neglected tropical disease. Lancet Glob Health. 2021; 9: e1618-e1622.

[11] World Bank report in 2020. Retrieved from: https://data.worldbank.org/indicator/NY.GDP.MKTP.CD. [Accessed and cited on 16 August 2023].

[12] Beardsley J, Denning DW, Chau NV, Yen NT, Crump JA, Day JN. Estimating the burden of fungal disease in Vietnam. Mycoses. 2015; 58 Suppl 5:101-6.

[13] Duong TN, Le MH, Beardsley J, Denning DW, Le NH, Nguyen BT. Updated estimation of the burden of fungal disease in Vietnam. Mycoses. 2023; 66:346-353.

[14] Thanh NT, Dat NT. Prevalence of HIV-associated Co-infections and Clinical Characteristics among HIV/AIDS Outpatients in the Context of Dolutegravir Roll-out Program in Vietnam. Texila International Journal of Public Health 2022. doi:10.21522/TIJPH.2013.10.02. Art021.

[15] Qin Y, Huang X, Chen H, Liu X, Li Y, Hou J, et al. Burden of Talaromyces marneffei infection in people living with HIV/AIDS in Asia during ART era: a systematic review and meta-analysis. BMC Infect Dis. 2020; 20:551.

[16] Al-Hatmi AMS, Al-Shuhoumi MA, Denning DW. Estimated Burden of Fungal Infections in Oman. J Fungi (Basel). 2020; 7(1):5.

[17] Mohsin J, Khalili SA, van den Ende AHGG, Khamis F, Petersen E, de Hoog GS, et al Talaromycosis in Oman in Advanced HIV: A Diagnostic Challenge Outside the Endemic Areas. Mycopathologia. 2017; 182:739-745.

[18] Castro-Lainez MT, Sierra-Hoffman M, LLompart-Zeno J, Adams R, Howell A, Hoffman-Roberts H, et al. *Talaromyces marneffei* infection in a non-HIV non-endemic population. IDCases. 2018; 12:21-24.

[19] Khwakhali US, Denning DW. Burden of serious fungal infections in Nepal. Mycoses. 2015; 58 Suppl 5:45-50.

[20] Taj-Aldeen SJ, Chandra P, Denning DW. Burden of fungal infections in Qatar. Mycoses. 2015; 58 Suppl 5:51-7.

[21] Huang YS, Denning DW, Shih SM, Hsiung CA, Wu UI, Sun HY, et al. Fungal Diseases in Taiwan-National Insurance Data and Estimation. J Fungi (Basel). 2019; 5:78.