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# Disease burden and demographic characteristics of mucormycosis: A nationwide population-based study in Taiwan, 2006–2017

Hsin-I Shih[1,2,3] | Yi-Ting Huang[1,2] | Chi-Jung Wu[4,5]

[1]Department of Emergency Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[2]School of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[3]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[4]National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Tainan, Taiwan

[5]Division of Infectious Diseases, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

**Correspondence**
Chi-Jung Wu, National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes; 5F., No.367, Sheng-Li Road, North District, Tainan,70456, Taiwan.
Email: wucj@nhri.edu.tw

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## Abstract

**Background:** Epidemiological knowledge of mucormycosis obtained from national population-based databases is scarce.

**Objectives:** This study aimed to depict the disease burden and demographics of mucormycosis in Taiwan by using the Taiwan National Health Insurance Research Database (NHIRD) and those of aspergillosis as a comparator.

**Methods:** Data from patients with either mucormycosis or aspergillosis from 2006 to 2017 identified with the International Classification of Diseases (ICD) codes were extracted from the NHIRD. The incidence, demographics and clinical data of both diseases were analysed.

**Results:** A total of 204 patients with mucormycosis and 2270 patients with aspergillosis who were hospitalised and treated with mould-active antifungals between 2006 and 2017 were identified. The average annual incidence of aspergillosis (0.81 cases per 100,000 population [0.81/100,000]) was 11-fold higher than that of mucormycosis (0.07/100,000). A significant increase in incidence was observed for aspergillosis (from 0.48/100,000 in 2006 to 1.19/100,000 in 2017, $p < .0001$) but not for mucormycosis (from 0.04/100,000 in 2006 to 0.11/100,000 in 2017, $p = .07$). The major underlying disease identified was diabetes mellitus (60.8%) for mucormycosis and malignant neoplasms (45.9%) for aspergillosis. The all-cause 90-day mortality rate was similar between mucormycosis and aspergillosis patients (39% vs. 37%, $p = .60$). For mucormycosis patients, multivariate analysis revealed that posaconazole use was associated with lower in-hospital mortality (aOR 0.38; 95% CI 0.15–0.97; $p = .04$).

**Conclusions:** Mucormycosis is an uncommon fungal disease in Taiwan, occurring mostly in diabetic patients. However, the incidence might be underestimated due to limited diagnostics. Continuous surveillance might aid in delineating the evolving features of mucormycosis.

KEYWORDS
aspergillosis, diabetes, epidemiology, haematological malignancy, incidence, mucormycosis, posaconazole, Taiwan

## 1 | INTRODUCTION

Mucormycosis is the most common invasive mould disease after aspergillosis. It is caused by members of the order *Mucorales*, which are thermotolerant fungi ubiquitously distributed in the environment, such as in decaying organic materials and soils. Patients usually acquire infection via inhalation, ingestion or direct inoculation of fungal spores. Those with diabetes mellitus, haematological malignancy, solid organ transplantation, corticosteroid use, iron overload and major trauma are at particular risk for developing mucormycosis.[1,2] Mucormycosis is characterised by its angioinvasive nature and is associated with substantial mortality. Rhino-orbital-cerebral and pulmonary forms are the most common manifestation of mucormycosis, followed by cutaneous, gastrointestinal and renal infection, and localised infection might progress to disseminated infection in severe cases.[1,2]

Epidemiological studies have demonstrated varied incidences and features of mucormycosis across different countries.[1,2] India was reported to have the highest estimated incidence of mucormycosis (14 cases per 100,000 population), with uncontrolled diabetes as the major risk factor, whereas lower incidences (0.06–0.2/100,000) were reported in most of the European countries, with haematological malignancy and transplantation as the major risk factors.[2] Nevertheless, the disease burden of mucormycosis described in the literature was mostly deduced from estimations based on available epidemiological data and modelling.[2] The currently available nationwide population-based incidence data were mainly from a French study, which used data extraction codes according to the International Classification of Diseases (ICD) from the French hospital information system.[3] It revealed an increasing trend in the incidence of mucormycosis from 0.07/100,000 in 1997 to 0.12/100,000 in 2006, with an average of 0.09/100,000 over the 10 years. This French incidence rate (0.09–1.2/100,000) was thus often used as a reference value for estimating the burden of mucormycosis in other countries.[4–6]

A comprehensive estimation of disease burden and identifying population at risk aids in determining public health measures and the diagnostic and therapeutic needs of the population. However, large-scale epidemiological research of mucormycosis in Asia is scarce and mostly limited to reports from single-centre or multicentre studies in India.[7] Taiwan is situated in East Asia, which belongs to the tropical and subtropical climate zone. It launched the National Health Insurance (NHI) in 1995, which covers more than 99% of the 23 million people who compose the Taiwanese population; therefore, Taiwan's National Health Insurance Research Database (NHIRD) could serve as a population-based database for large-scale, healthcare research.[8] Using the NHIRD, studies revealed an increase in the immunocompromised population and in diabetes prevalence over the years and a significant increase in the incidence of invasive pulmonary aspergillosis from 0.94 cases in 2002 to 2.06 cases in 2011 per million population ($p < .0001$),[9–13] while the incidence of mucormycosis remained undescribed. Therefore, this study aimed to delineate the temporal trend of disease burden and demographic characteristics of mucormycosis in Taiwan during 2006–2017 based on the NHIRD using those of aspergillosis as comparators.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and database

We conducted a nationwide, population-based retrospective cohort study that investigated the incidence, demographic and clinical characteristics of mucormycosis and aspergillosis that occurred between 2006 and 2017 in Taiwan by analysing data from the NHIRD. The NHIRD comprises secondary data released for research purposes, which includes information on patient demographics, outpatient visits, hospital admission, prescribed medication, interventional procedures and up to four diagnoses for outpatients and up to five discharge diagnoses for inpatients. Diseases are coded based on the ICD, Ninth Revision, Clinical Modification (ICD-9-CM) code from 2006 to 2015, and ICD-10-CM code from 2016 to 2017. Personal information was deidentified by the Taiwan Health and Welfare Data Science Centre (HWDC) but could be anonymously linked to the official Taiwan Death Registry dataset, which was also assessed in this study to obtain the patient outcome (mortality). According to the regulation of HWDC, case numbers lower than three were not allowed to be reported in the analyses to avoid reidentification.

### 2.2 | Study subjects and definitions

Patients with either mucormycosis or aspergillosis from 2006 to 2017 were identified if they had received an ICD code for either disease (not restricted to primary and secondary diagnosis), and the ICD codes for both diseases are provided in Table Table S1. To ensure the accuracy of disease diagnosis, only patients who were hospitalised and treated with either oral and/or intravenous mould-active drugs, including amphotericin B (both deoxycholate and lipid formulation), itraconazole, voriconazole, posaconazole, anidulafungin, micafungin and caspofungin, were enrolled. The flowchart in Figure 1 summarises the study selection process. The index date was defined as the first date of hospital admission during which mucormycosis or aspergillosis was diagnosed. The annual case number, demographics, comorbidities, medical treatment and all-cause mortality of patients were assessed. Comorbidities that were coded in at least two outpatient visits or one discharge diagnosis for inpatients within 1 year preceding the index date were included for analyses, which included autoimmune disease, chronic heart failure, chronic obstructive pulmonary disease (COPD), diabetes mellitus, human immunodeficiency virus (HIV) infection, liver cirrhosis and malignant neoplasms, including both haematological cancer and solid cancer. End-stage renal disease (ESRD) was coded if the patients received regular dialysis within 90 days preceding the index admission. The medical treatment assessed included antineoplastic chemotherapy and corticosteroids within 90 days

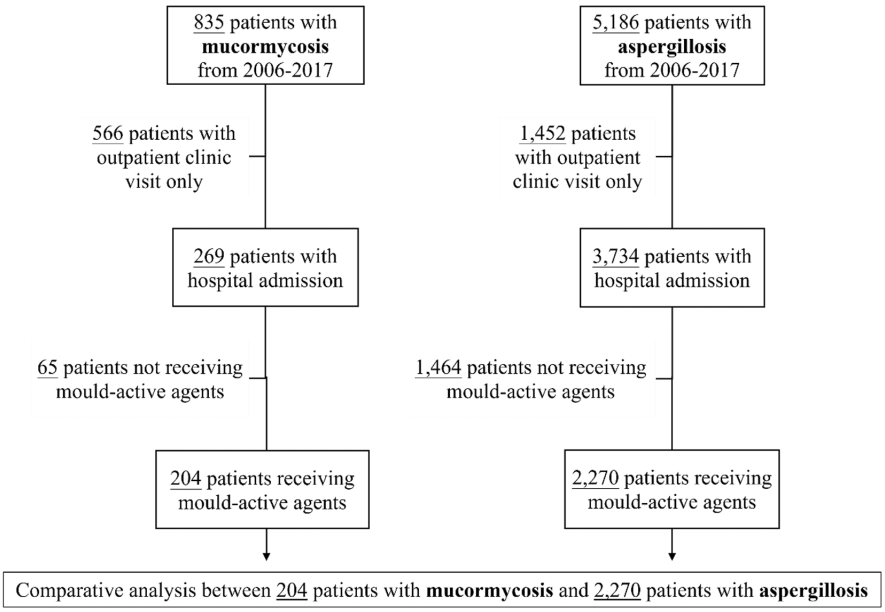
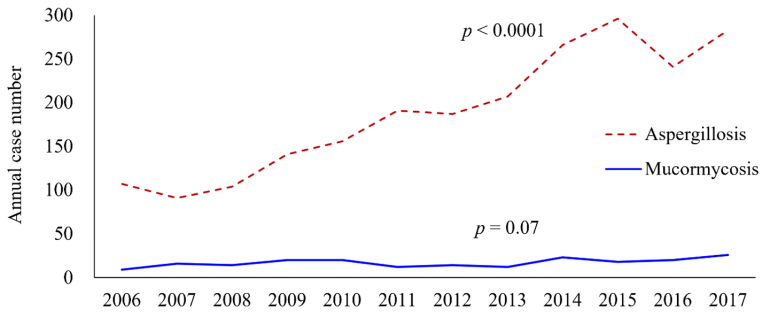



**FIGURE 1** Flowchart summarising the study selection process in this study




| Annual incidence (cases per 100,000 population) | | | | | | | | | | | | | Average |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Aspergillosis | 0.48 | 0.40 | 0.45 | 0.61 | 0.68 | 0.82 | 0.80 | 0.88 | 1.13 | 1.25 | 1.01 | 1.19 | 0.81 |
| Mucormycosis | 0.04 | 0.07 | 0.06 | 0.09 | 0.09 | 0.05 | 0.06 | 0.05 | 0.10 | 0.08 | 0.08 | 0.11 | 0.07 |

**FIGURE 2** Annual case numbers and incidence of mucormycosis compared with those of aspergillosis during 2006–2017

preceding and during the index admission, transplantation (bone marrow transplantation and organ transplantation) within 1 year preceding and during the index admission and mould-active antifungals during the index admission. The severity of comorbidity was scored based on the Charlson Comorbidity Index (CCI).[14] The ICD codes for comorbidities and medical treatment are provided in Table Table S1, and the Anatomical Therapeutic Chemical (ATC) Classification codes for mould-active antifungals and corticosteroids are provided in Table S2.

All-cause in-hospital mortality was defined as death during the index admission or within 72 hours after discharge. All-cause 30-day and 90-day mortality was defined as death at 30 days and 90 days after discharge, respectively.

## 2.3 | Statistical analysis

All statistical analyses were performed with SAS 9.4 software (SAS Institute). The temporal trend of disease incidence was examined using the trend test. Demographic and clinical data of mucormycosis and aspergillosis were compared, and factors associated with mortality in either disease were examined by both univariate analysis and multivariate analyses using the backward elimination method. The chi-square test was used for categorical variables, and Student's t test was used for continuous variables. Survival probability was estimated for each group using the Kaplan–Meier method and compared using the log-rank test. All statistical tests were 2-sided, and $p$ values <.05 were considered statistically significant.

This study was approved by the institutional review board (IRB) of National Chen-Kung University Hospital and National Health Research Institute (registration numbers: A-ER-108-479 and EC1070104-E) and the requirement to obtain informed consent was waived.

# 3 | RESULTS

Over the 12-year study period, the population covered by Taiwan's NHI increased from 22.4 million in 2006 to 23.8 million in 2017, exceeding 99% of the total population in Taiwan. A total of 204 patients with mucormycosis and 2270 patients with aspergillosis who were hospitalised and treated with mould-active antifungals from

2006 to 2017 were identified and extracted from the NHIRD for further analyses (Figure 1). Overall, the annual incidence of mucormycosis (range 0.04–0.11/100,000) was lower than that of aspergillosis (range 0.40–1.25/100,000), and the average annual incidence of aspergillosis (0.81/100,000) was approximately 11-fold higher than that of mucormycosis (0.07/100,000) (Figure 2). Notably, the incidence of aspergillosis increased significantly over the years, from 0.48/100,000 in 2006 to 1.19/100,000 in 2017 ($p < .0001$). Although the incidence of mucormycosis also increased from 0.04/100,000 in 2006 to 0.11/100,000 in 2017, the increase did not reach statistical significance ($p = .07$).

Patients with mucormycosis and patients with aspergillosis were old-aged (mean age 59.4- and 57.6-year-old, respectively), and most patients were male (67.2% and 64.3%, respectively). Diabetes mellitus (60.8% vs. 23.8%; adjusted odds ratio (aOR) 4.30, 95% confidence interval (CI) 3.17–5.82, $p < .0001$) was more commonly associated with mucormycosis, whereas malignant neoplasms (22.1% vs. 45.9%, $p < .0001$), including haematological malignancy (16.7% vs. 34.2%), solid cancer (7.8% vs. 16.3%) and COPD (14.2% vs. 23.9%, $p = .0002$), were more commonly associated with aspergillosis (Table 1). HIV infection was identified in less than three (<1%) patients with mucormycosis and in 32 (1.4%) patients with aspergillosis.

The all-cause in-hospital, 30-day and 90-day mortality rates did not differ significantly between mucormycosis and aspergillosis (22.1% vs. 22.3%, $p = .93$; 29.9% vs. 26.9%, $p = .35$; 38.7% vs. 37.1%, $p = .64$) (Table 1). Kaplan–Meier survival curves revealed similar survival probability for both diseases at 90 days after discharge ($p = .60$) (Figure 3A). Of 204 patients with mucormycosis, 187 (91.6%) patients had received *Mucorales*-active agents with either amphotericin B or posaconazole. In the multivariate analysis which examined factors of gender, age, underlying diseases, chemotherapy, corticosteroids use and prescribed antifungal agents, posaconazole use was found to be associated with lower in-hospital mortality (aOR

**TABLE 1** Demographic and clinical data of patients with mucormycosis and patients with aspergillosis from 2006 to 2017

| | Case no. (%) | | Univariate | Multivariate | |
|---|---|---|---|---|---|
| Variables | Mucormycosis, $n = 204$ | Aspergillosis, $n = 2270$ | $p$ value | aOR (95% CI) | $p$ |
| Male sex | 137 (67.2) | 1459 (64.3) | .50 | | |
| Age, mean ± SD (years) | 59.4 ± 16.2 | 57.6 ± 19.9 | .14 | | |
| Age ≥ 50 y.o. | 152 (74.5) | 1615 (71.1) | .57 | | |
| Age ≥ 65 y.o. | 86 (42.2) | 893 (39.3) | .70 | | |
| Underlying conditions within 1 year prior to admission | | | | | |
| Autoimmune disease | 13 (6.4) | 161 (7.1) | .70 | | |
| Chronic heart failure | 46 (22.5) | 304 (13.4) | .0003 | | |
| COPD | 29 (14.2) | 542 (23.9) | .002 | 0.46 (0.30–0.70) | .0002 |
| Corticosteroids use (within 90 days) | 127 (62.3) | 1445 (63.7) | .69 | | |
| Diabetes mellitus | 124 (60.8) | 540 (23.8) | <.0001 | 4.30 (3.17–5.82) | <.0001 |
| ESRD on dialysis (within 90 days) | 3 (1.5) | 21 (0.9) | .45 | | |
| Liver cirrhosis | 27 (13.2) | 208 (9.2) | .06 | | |
| Malignant neoplasm | 45 (22.1) | 1042 (45.9) | <.0001 | 0.41 (0.29–0.58) | <.0001 |
| Haematological cancer | 34 (16.7) | 776 (34.2) | <.0001 | | |
| Solid organ cancer | 16 (7.8) | 370 (16.3) | .001 | | |
| CCI ≥3 | 86 (42.2) | 983 (43.3) | .75 | | |
| Treatment prior to and during admission | | | | | |
| Antineoplastic chemotherapy (within 90 days) | 28 (13.7) | 700 (30.8) | <.0001 | | |
| Transplantation (within one year) | 10 (4.9) | 115 (5.1) | .92 | | |
| Bone marrow transplant | 4 (2.0) | 75 (3.3) | .30 | | |
| Solid organ transplant | 6 (2.9) | 43 (1.9) | .30 | | |
| All-cause mortality | | | | | |
| In-hospital | 45 (22.1) | 507 (22.3) | .93 | | |
| 30-day | 61 (29.9) | 610 (26.9) | .35 | | |
| 90-day | 79 (38.7) | 842 (37.1) | .64 | | |

Abbreviations: aOR, adjusted odds ratio; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; SD, standard deviation.

0.38; 95% CI 0.15–0.97; $p$ = .04), whereas voriconazole use was associated with in-hospital mortality (aOR 3.31; 95% CI 1.48–7.39; $p$ = .003) (Table 2). Kaplan–Meier survival analysis also demonstrated that posaconazole use during hospitalisation was associated with a higher survival probability at 90 days after discharge ($p$ = .04), whereas voriconazole use was associated with a lower survival probability ($p$ = .02) (Figure 3B,C). Of 2270 patients with aspergillosis, all patients had received mould-active agents. Multivariate analysis revealed that COPD, haematological cancer and antineoplastic chemotherapy were associated with lower in-hospital mortality, whereas age ≥ 65 y.o., CCI ≥3 and use of amphotericin B or corticosteroids were associated with in-hospital mortality (Table S3).

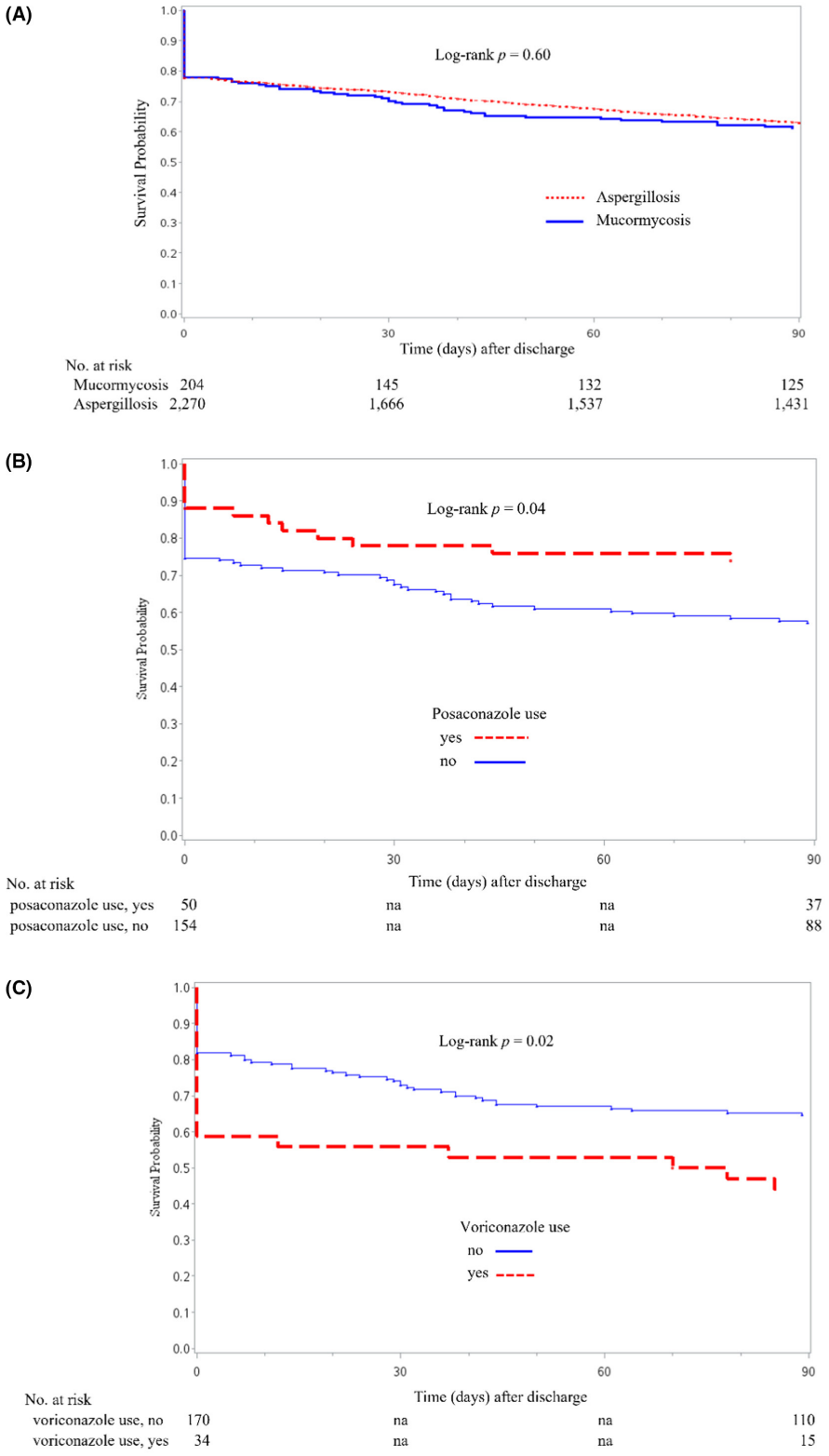



FIGURE 3 Kaplan–Meier survival curves at 90 days after discharge according to (A) diagnosis (mucormycosis vs. aspergillosis), (B) posaconazole use in mucormycosis and (C) voriconazole use in mucormycosis (na, data reporting not allowed)

**TABLE 2** Clinical data and factors associated with all-cause in-hospital mortality among patients with mucormycosis from 2006 to 2017

| | Mucormycosis cases, *n* = 204 | | | | |
|---|---|---|---|---|---|
| | | | Univariate | Multivariate | |
| Variables, no. (%) | Survivor, *n* = 159 | Non-Survivor, *n* = 45 | *p* | aOR (95% CI) | *p* |
| Male sex | 109 (68.6) | 28 (62.2) | .43 | | |
| Age, mean ± SD (years) | 58.4 ± 16.6 | 62.9 ± 14.3 | .10 | | |
| Age ≥ 50 y.o. | 116 (73.0) | 36 (80.0) | .34 | | |
| Age ≥ 65 y.o. | 64 (40.3) | 22 (48.9) | .30 | | |
| Underlying conditions within 1 year prior to admission[a] | | | | | |
| Autoimmune disease | 9 (5.7) | 4 (8.9) | .44 | | |
| Chronic heart failure | 33 (20.8) | 13 (28.9) | .25 | | |
| COPD | 24 (15.1) | 5 (11.1) | .50 | | |
| Corticosteroids use (within 90 days) | 101 (63.5) | 26 (57.8) | .48 | | |
| Diabetes mellitus | 97 (61.0) | 27 (60.0) | .90 | | |
| Liver cirrhosis | 23 (14.5) | 4 (8.9) | .33 | | |
| Malignant neoplasm | 32 (20.1) | 13 (28.9) | .21 | | |
| Haematological cancer | 24 (15.1) | 10 (22.2) | .26 | | |
| Solid organ cancer | 12 (7.5) | 4 (8.9) | .77 | | |
| CCI ≥3 | 67 (42.1) | 19 (42.1) | .99 | | |
| Treatment within 90 days prior to and during admission | | | | | |
| Antineoplastic chemotherapy | 21 (13.2) | 7 (15.6) | .69 | | |
| Treatment during admission | | | | | |
| Corticosteroids use | 111 (69.8) | 34 (75.6) | .45 | | |
| Antifungal agents[b] | | | | | |
| Amphotericin B | 143 (89.9) | 41 (91.1) | .82 | | |
| Posaconazole | 44 (27.7) | 6 (13.3) | .05 | 0.38 (0.15–0.97) | .04 |
| Voriconazole | 20 (12.6) | 14 (31.1) | .004 | 3.31 (1.48–7.39) | .003 |
| Anti-*Aspergillus*-only | 49 (30.8) | 18 (40.0) | .25 | | |
| *Mucorales*-active | 149 (93.7) | 42 (93.2) | .93 | | |
| Mould-active agents | 159 (100.0) | 45 (100.0) | na | | |

Abbreviations: aOR, adjusted odds ratio; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; na, nonapplicable; SD, standard deviation.

[a]The number of patients receiving haemodialysis or transplantation was less than three in some cells, and thus the data regarding end-stage renal disease and transplantation was not provided.

[b]Anti-*Aspergillus*-only agents include itraconazole, voriconazole, anidulafungin, caspofungin and micafungin; *Mucorales*-active agents include posaconazole and amphotericin B; mould-active agents include amphotericin B, itraconazole, voriconazole, posaconazole, anidulafungin, caspofungin and micafungin.

## 4 | DISCUSSION

Our study hereby presented the temporal trend of disease burden and demographic characteristics of mucormycosis during a 12-year period (2006–2017) in Taiwan by analysing nationwide, population-based data. With aspergillosis as a comparator, four major findings were revealed: (1) a 12-year average incidence of 0.07/100,000 and an incidence of 0.11/100,000 in 2017 for mucormycosis were documented; (2) the major underlying disease identified was diabetes mellitus for mucormycosis and malignant neoplasm for aspergillosis; (3) a significant increase in incidence was observed for aspergillosis but was not evident for mucormycosis and (4) posaconazole use was associated with a better survival probability in mucormycosis.

The incidence of mucormycosis in Taiwan (0.11/100,000 in 2017) is similar to that reported in France in 2006 (0.12/100,000), both based on nationwide population-based data.[3] As national data on fungal infection were not available in most countries, the Leading International Fungal Education (LIFE) program led by David Denning (http://www.LIFE-worldwide.org) has made great efforts to estimate the global burden of serious fungal infection, including mucormycosis, by using the available epidemiological data (the population at risk, published literature) and modelling. In addition to the French

incidence (0.09–0.12/100,000), an incidence rate of 0.2/100,000 was also used as a general literature value for incidence estimation of mucormycosis in some countries.[15–18] The estimated incidence rates in different countries, mostly from the data of the LIFE program, have been comprehensively summarised in a review article by Prakash et al.[2] In this review, the incidences of mucormycosis in most countries were within the range of 0.06–0.2/100,000 and were as follows: Europe (Greece 0.06, United Kingdom 0.09, Norway 0.1 and Ireland 0.2), North America (Canada 0.12 and USA 0.3), Asia (Korea 0.14, Japan 0.2 and Thailand 0.2), Africa (Algeria, Kenya, Malawi, Nigeria 0.2), Russia (0.16) and Australia (0.06), whereas India (14), Pakistan (14) and Portugal (9.5) ranked as the countries with the highest incidences. The incidence of mucormycosis in Taiwan was also in line with estimated incidences in most countries within the same period, and hence provided the second and latest nationwide data, after the French study, for estimating the disease burden of mucormycosis.

Risk factors and underlying comorbidities for mucormycosis vary considerably with geographical area.[1] Diabetes was the leading underlying condition in India (57–74%), in contrast to haematological malignancies in Europe (44%), including France (50%) and Italy (62%), and Australia (49%).[1] As observed in India, we found in Taiwan that diabetes (61%) predominated over malignant neoplasms (22%), including haematological malignancy (17%), as the major underlying disease in mucormycosis. This feature was further contrasted with aspergillosis, for which underlying malignant neoplasms (46%), including haematological malignancies (34%), predominated over diabetes (24%). According to the IDF Diabetes Atlas in 2021, India (9.6%) and Taiwan (9.7%) have higher age-adjusted comparative diabetes prevalence in adults 20–79 years (though India might have a number of undiagnosed diabetes) than the European countries (7.0%) and Australia (6.4%).[19] On the contrary, the Global Burden of Disease (GBD) 2017 study revealed that Taiwan is one of the countries with higher leukaemia prevalence and shared similar prevalence with France, whereas India has lower leukaemia prevalence.[20] Experts hypothesized one of the possible reasons for the high occurrence of mucormycosis in India to be the abundance of thermotolerant and thermophilic *Mucorales* in the environment due to a hot and humid climate.[7] Taiwan has a tropical and subtropical monsoon climate with wet and humid summers, which might allow ubiquitous growth of *Mucorales* in the environment. Collectively, it is presumed that community residents with diabetes in Taiwan would have a higher probability of inhaling spores of pathogenic *Mucorales*, leading to invasive disease when immune responses compromise. Further environmental surveillance would be helpful to elucidate this hypothesis. From a clinical perspective, these findings suggested that medical staff in Taiwan must remain vigilant of the occurrence of mucormycosis in diabetic patients without haematological malignancy, especially those presenting invasive sinusitis or pneumonia not responding to antibacterial therapy.

Our study, along with reports elsewhere, demonstrated that the incidences of aspergillosis were generally 10–30 times higher than those of mucormycosis.[2] Notably, the incidence of mucormycosis in Taiwan remained stable over the years, in contrast to an apparent rising trend in aspergillosis. The galactomannan (GM) antigen test was approved by the United States Food and Drug Association (FDA) for diagnosing *Aspergillus* infection and was introduced into Taiwan in 2004. Based on Taiwan's NHIRD, studies revealed that the increase in the incidence of invasive pulmonary aspergillosis was positively correlated with the increase in the use of GM testing during 2002–2011.[13] Moreover, in Taiwan, the incidences for all cancers doubled from 1988 to 2016, the crude annual incidence of acute myeloid leukaemia increased from 2.78/100,000 in 2006 to 3.21/100,000 in 2015, and the annual number of haematopoietic stem cell transplants performed increased from 381 in 2006 to 521 in 2015.[9–11] Therefore, the rising incidence of aspergillosis in Taiwan might be in part attributed to the clinical application of new diagnostics and an expanded susceptible population. In addition, the prevalence of diabetes, the major underlying disease of mucormycosis, in patients aged 20–79 years increased by 41% from 2005 to 2014.[12] Given that there were increasing susceptible hosts (diabetes and malignancy) in Taiwan and observed rising trends of mucormycosis in France and India,[2,3] we initially expected a similar upwards trend of mucormycosis to be revealed in this study, but it turned out that our data did not support this assumption. From 2006 to 2017 in Taiwan, the diagnosis of mucormycosis mainly depended on conventional culture methods and histopathological examination of biopsy tissue from infected sites demonstrating broad-based, pauciseptate ribbon-like fungal elements consistent with *Mucorales*. However, their diagnostic sensitivity or feasibility are suboptimal for diagnosing mucormycosis. A multicentre study from Taiwan found that the culture yield rate was only 37% for invasive mucormycosis compared with 67% for invasive aspergillosis.[21] Furthermore, patients with mucormycosis might have a rapidly deteriorated and fulminant fatal course, which makes timely diagnosis by fungal culture or tissue biopsy less likely or makes laboratory reports available only postmortem. Even in critical patients with a less fulminant course, collecting samples from deep tissue is also challenging. Additionally, there is no commercially available antigen testing to detect *Mucorales* in blood or respiratory samples as a noninvasive diagnostic approach so far. Taken together, the incidence of mucormycosis here might probably be underestimated due to limited diagnostic tools, which further underlines the unmet need for improved diagnostics of mucormycosis.

Amphotericin B, posaconazole and the new triazole isavuconazole are recommended as antifungals for the treatment of aspergillosis and mucormycosis, while voriconazole is a recommended drug for aspergillosis but not mucormycosis, as it is inactive against *Mucorales*.[22,23] Posaconazole was approved for clinical use by the U.S. FDA in 2006 and has been available in Taiwan since 2010. An association of posaconazole use with a higher survival probability demonstrated here supported its clinical efficacy in treating mucormycosis. However, confounding bias might exist. For instance, patients who had the chance to receive posaconazole might have a less fulminant disease course or lower disease severity, which allowed

obtaining clinical samples for fungal culture or histopathological examination to achieve accurate aetiological diagnosis and prescribe targeted antifungal therapy accordingly. Isavuconazole was approved for clinical use by the U.S. FDA in 2015 and available in Taiwan since 2021, and hence, its impact on clinical outcome could not be assessed here. However, future studies comparing the clinical efficacy of posaconazole and isavuconazole would be appealing, as they exhibit different in vitro activities against certain members of *Mucorales*, such as *Cunninghamella bertholletiae*.[24]

This study has some limitations. First, given the inherent limitations of the ICD system and lack of detailed clinical, laboratory and radiological data in the NHRID, the accuracy of diagnosis was suboptimal, and disease classification as proven and probable invasive fungal disease based on the European Organisation for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSG) definitions could not be made.[25] In addition, ICD-9 did not include assignment of infected organ yet, neither for mucormycosis nor for aspergillosis, and thus, correlation between severity of disease and outcome could not be investigated in this study. To confirm diagnosis, we enrolled only patients who had ever received mould-active antifungal(s), indicating high clinical suspicion of invasive fungal disease. It is well understood that by this restriction, patients diagnosed post-mortem without systemic antifungal treatment were also excluded from disease burden calculation. Second, the clinical efficacy of antifungal prescription evaluated from different aspects (aetiological agents, time to initiation of antifungal therapy, monotherapy vs. combination therapy and antifungal duration) could not be assessed due to limitations of the data structure. A multicentre study enrolling a large number of patients with detailed clinical information is needed to elucidate these issues.

In conclusion, the nationwide population-based database revealed that mucormycosis is an uncommon fungal disease in Taiwan that occurs mostly in diabetic patients. An increasing trend in incidence was not evident, but the incidence might be underestimated due to limited diagnostics for mucormycosis. With increasing number of susceptible hosts, availability of isavuconazole and global and domestic efforts to raise clinical awareness, continuous surveillance might aid in delineating the evolving features of mucormycosis.

## AUTHOR CONTRIBUTIONS

Shih H.I. and Wu C.J. involved in conceptualization, funding acquisition and writing—review and editing. Huang Y.T. and Shih H.I. involved in data curation. Huang Y.T. involved in Formal analysis. Shih H.I., Huang Y.T. and Wu C.J. involved methodology and validation. Shih H.I., Huang Y.T. and Wu C.J. involved in writing—original draft.

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## CONFLICT OF INTEREST

None to declare.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

*Chi-Jung Wu* https://orcid.org/0000-0002-9607-9088

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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