

# MORTALITY AND ITS RISK FACTORS AMONG IN-PATIENTS WITH INVASIVE ASPERGILLOSIS TREATED WITH VORICONAZOLE

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**Abstract.** Invasive aspergillosis (IA), a cause of mortality in immunocompromised patients, is treated in Thailand with voriconazole. We aimed to determine the overall and 90-day mortality rates among IA in-patients treated with voriconazole and the factors significantly associated with mortality in order to guide empiric treatment of IA at Rajavithi Hospital, Bangkok, Thailand. We retrospectively reviewed the charts of all in-patients treated at the study hospital for IA with voriconazole during 2015-2020. We evaluated selected factors to determine significant associations with mortality. A total of 33 subjects were included in our study; 55% female ( $n = 18$ ), of which 9 patients (27%) died. The number of study subjects was far fewer than the minimum number of subjects calculated to be needed for statistical significance in our study. On univariate analysis male sex ( $p = 0.01$ ) and acute renal failure ( $p = 0.095$ ) were significantly ( $p < 0.1$ ) associated with mortality. On multivariate analysis, male sex ( $p = 0.013$ ) was the only factor significantly ( $p < 0.05$ ) associated with mortality. It should be noted that these results may not reflect actual significance due to the overall number of study subjects not reaching the minimum calculated number. In summary, the mortality rate among study subjects was high, especially among males. We conclude there is a need to identify methods to reduce mortality among patients with IA at the study institution. Further studies are need to determine what methods can reduce mortality in this study population, such as changing the current treatment regimen with voriconazole.

**Keywords:** invasive aspergillosis, voriconazole, 90-day mortality, risk factor related mortality

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## INTRODUCTION

Invasive aspergillosis (IA) is caused by *Aspergillus* spp (Rudramurthy *et al*, 2019). There are 180 species of *Aspergillus*, a type of fungus, of which 40 have been shown to cause disease in humans (CDC, 2021). The most common *Aspergillus* species causing aspergillosis in humans is *Aspergillus fumigatus* (CDC, 2021). Other species reported to cause aspergillosis include *A. flavus*, *A. terreus* and *A. niger* (CDC, 2021)

*Aspergillus* spp can be found in soil, air, plants and on human skin (Merad *et al*, 2021). People inhale the spores which do not usually cause disease (CDC, 2021) except in the immunocompromised or in people with underlying lung disease (Denning and Stevens, 1990, Rudramurthy *et al*, 2019). Aspergillosis usually causes lung or sinus infections in humans (CDC, 2021). Aspergillosis may be disseminated in humans affecting other organs (CDC, 2021). IA is a type of aspergillosis consisting of a serious infection that usually occurs in the immunocompromised (Baddley, 2011). The presentation of IA depends on the organ system affected and the immune system of the individual (Barnes and Marr, 2006).

The types of immunocompromised states that increase the risk for contracting IA include acquired immunodeficiency syndrome (AIDS),

receiving chemotherapy, receiving high doses of corticosteroids, having received a donated organ or having a stem cell transplant, taking some types of immunosuppressive drugs, having chronic obstructive pulmonary disease (COPD), having diabetes mellitus (DM), having tuberculosis (TB), having hepatic impairment or having prolonged neutropenia (CDC, 2021, Baddley, 2011).

The number of patients in Thailand with IA is increasing (Hsu *et al*, 2015). Voriconazole is listed as first-line treatment for IA by The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) 2017 recommendations and is followed in many countries, such as Switzerland and the United Kingdom (Ullmann *et al*, 2018) and is recommended by the Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America (IDSA) (Patterson *et al*, 2016). Voriconazole is available and is the drug of choice for IA in Thailand (Chayakulkeeree *et al*, 2014). However, there is little data in Thailand regarding mortality and its associated factors among patients treated for IA with voriconazole. In this study we aimed to determine the mortality and its associated factors among IA patients treated with voriconazole in order to guide empiric treatment of IA at Rajavithi Hospital, Bangkok, Thailand.

## MATERIALS AND METHODS

### Study subjects

We retrospectively reviewed the charts of patients admitted to Rajavithi Hospital, diagnosed with IA and treated with voriconazole during 1 June 2015 - 1 June 2020. We determined the overall and 90-day mortality rate among in-patients treated with voriconazole and factors significantly associated with mortality. Exclusion criteria for study subjects were having incomplete data, not being treated with voriconazole and not being diagnosed with IA. The minimum sample size calculated to be needed for this study using the Wayne WD formula (Daniel and Cross, 2013) was determined to be 310 subjects.

### Data collection

The clinical data gathered was general information and the outcome of treatment. This general information was type of specimen used to diagnose IA, presence or absence of selected study factors and location of infection. A literature review revealed factors associated with mortality in IA cases were: hematological malignancies (leukemia, lymphoma and multiple myeloma), solid organ, stem cell or allogenic bone marrow transplantation, chronic obstructive pulmonary disease, human immunodeficiency virus infection, corticosteroid treatment, tracheal infection, empirical treatment with itraconazole, diabetes mellitus, respiratory failure, pulmonary

hemorrhage, viral hepatitis, hepatic steatosis, chronic granulomatosis, alcoholic hepatitis, acute liver failure, cirrhosis, being aged  $\geq 65$  years, end-stage renal disease (ESRD) and male sex (Patterson *et al*, 2016, Jutivorakool and Tirastittam, 2019, Choi *et al*, 2008, Garcia-Vidal *et al*, 2015, Falcone *et al*, 2011). Of these factors reported in the literature, we chose the following factors to evaluate for a potential association with mortality: male sex, being aged  $\geq 65$  years, having hematologic malignancy, having diabetes mellitus, having acute renal failure, having respiratory failure and ESRD. We determined the overall and 90-day mortality rates.

This study was reviewed and approved Ethics Committee of Rajavithi Hospital (No. 64127).

### Statistical analysis

In this study, we used descriptive statistics to calculate the overall and 90-day mortality rate. We used univariate ( $p < 0.1$ ) and multivariate ( $p < 0.05$ ) analysis to evaluate selected factors potentially associated with mortality using 95% confidence intervals (CI). We carried out the statistical calculations using the Statistical Package for the Social Sciences (SPSS), version 21.0 (IBM, Armonk, NY).

## RESULTS

A total of 33 subjects were included in our study; 46% male. Seventy-four

percent of subjects were aged  $\geq 65$  years. This was far fewer than the minimum of 310 subjects calculated to be needed for this study to reach statistical significance and accurately reflect the study population. Of the 33 subjects, 9 (27%) died (8 males), 6 (18%) within 90 days of diagnosis (Figs 1, 2 and 3). Of the 9 subjects who died, 6 (67%) had an underlying hematological malignancy, 3 (33%) had diabetes, 3 (33%) were on high dose steroids, 3 (33%) had acute renal failure, 2 (22%) had ESRD, 1 (11%) had respiratory failure and 1 (11%) had initially been treated empirically with itraconazole.

The IA infections in our study subjects involved the pulmonary tract, sinuses and eyes in 64% ( $n = 21$ ), 33% ( $n = 11$ ) and 3% ( $n = 1$ ), respectively (Table 1).

### Factors associated with mortality

On univariate analysis, factors significantly associated with mortality were male sex (odds ratio (OR) = 0.051; 95% confidence interval (CI): 0.005-0.492;  $p = 0.01$ ) and acute renal failure (OR = 0.182; 95% CI: 0.025-1.349;  $p = 0.095$ ) (Table 2). On multivariate analysis, the only factor significantly (adjusted OR = 0.045; 95% CI: 0.004-0.520;  $p = 0.013$ ) associated with mortality was male sex (Table 2).

## DISCUSSION

In our study, the overall mortality rate was 27% and the 90-day mortality

rate was 18%. Our study result is similar to the 29% mortality rate reported in a study from Taiwan (Sun *et al*, 2017).

In our study, male subjects were significantly more likely to die of IA than female subjects, which is in contrast to a study from Spain that reported females were more likely to die from IA (Garcia-Vidal *et al*, 2015). Factors previously reported to be significantly associated with mortality in patients with IA include: having a hematological malignancy, undergoing mechanical ventilation, having respiratory failure and having a tracheal infection (Jutivorakool and Tirastittam, 2019; Garcia-Vidal *et al*, 2015; Cornillet *et al*, 2006; Sun *et al*, 2017). Possible reasons why we did not find these associations in our study include, our small study sample, differences by region, differences in numbers of study subjects, duration of the study, differences in the organs infected, different co-morbidities and different complications.

A limitation of our study was not considering subject symptoms, not having the results of fungal cultures confirming the diagnosis of IA and our small study size not reaching the minimum number of subjects calculated to be required to reach significance. Larger studies covering multiple institutions reaching the minimum number of subjects needed may provide more accurate information on mortality and mortality associated factors.

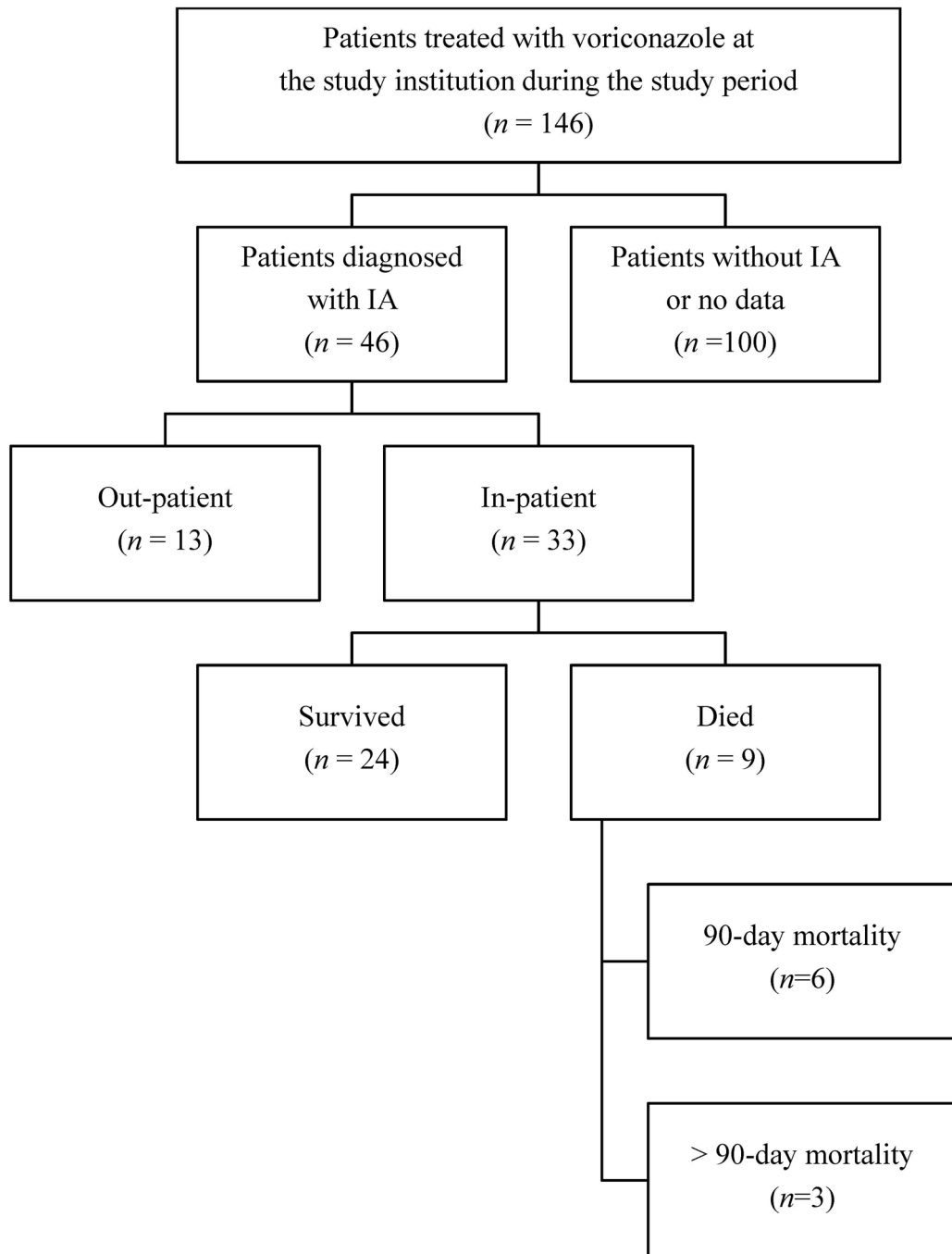


Fig 1 - Selection of study subjects  
IA: invasive aspergillosis

### Overall mortality

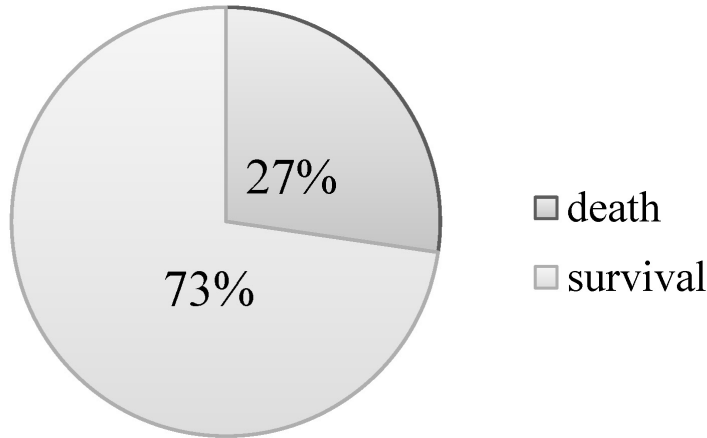


Fig 2 - Overall mortality rate of study subjects

### 90-day mortality

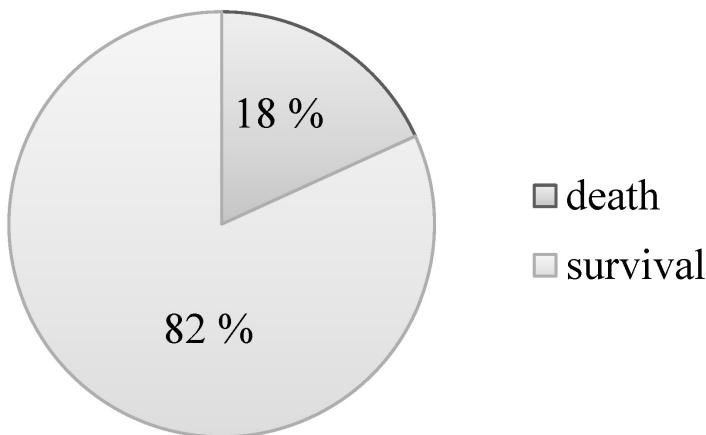


Fig 3 - Ninety-day mortality rate of study subjects

In summary, we had a high mortality rate in our study and the only factor significantly associated with it was male sex, which is non-modifiable. It is unclear if change from the use of voriconazole to another antifungal would improve this mortality rate or not. The mortality rate in our study was lower than many reported in the literature and the single factor associated with mortality in our study, male sex, was also different than that reported in other studies. Our study was severely limited by the fact we only reached 10% of the minimum number of study subjects calculated to be needed for the study. A larger, multi-center study would provide more useful data. Further studies are needed to determine what changes are needed to reduce this mortality rate further.

Table 1

Demographic characteristics of study subjects

Variables	Survived (N = 24)	Died (N = 9)	Total (N = 33)
Gender, <i>n</i> (%)			
Female	17 (70)	1 (11)	18 (55)
Male	7 (29)	8 (89)	15 (46)
Age, <i>n</i> (%)			
<65 years old	6 (25)	3 (33)	9 (27)
≥65 years old	18 (75)	6 (67)	24 (74)
Site of infection, <i>n</i> (%)			
Pulmonary	15 (63)	6 (67)	21 (64)
Sinus	8 (33)	3 (33)	11 (33)
Eye	1 (4)	0 (0)	1 (3)
Underlying diseases, <i>n</i> (%)			
Hematologic malignancy	9 (38)	6 (67)	15 (46)
Diabetes mellitus	10 (42)	3 (33)	13 (39)
Acute renal failure	2 (8)	3 (33)	5 (15)
High dose corticosteroids	0 (0)	3 (33)	3 (9)
Respiratory failure	1 (4)	1 (11)	2 (6)
ESRD	3 (13)	2 (22)	5 (15)
Solid organ transplantation	2 (8)	0 (0)	2 (6)
HIV infection	1 (4)	0 (0)	1 (3)
Empiric treatment with itraconazole	0 (0)	1 (11)	1 (3)

ESRD: end stage renal disease; HIV: Human immunodeficiency virus

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Table 2  
Univariate analysis and multivariate analysis of variables potentially associated with mortality among study subjects

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	adjusted OR	95% CI	p-value
Male sex	0.051	0.005-0.492	0.010 <sup>a</sup>	0.045	0.004-0.520	0.013 <sup>b</sup>
Age ≥65 years	1.900	0.347-10.404	0.459			
Hematologic malignancy	0.300	0.060-1.506	0.144			
Diabetes mellitus	1.429	0.287-7.118	0.663			
Acute renal failure	0.182	0.025-1.349	0.095 <sup>a</sup>	0.137	0.009-1.998	0.146
Respiratory failure	0.348	0.019-6.325	0.473			
ESRD	0.500	0.069-3.633	0.493			

<sup>a</sup> significance at  $p < 0.1$ ; <sup>b</sup> significance at  $p < 0.05$

adjusted OR: adjusted odds ratio; CI: confidence interval; ESRD: end stage renal disease; OR: odds ratio

## CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

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