*Original Article*

# Prevalence and Clinical Risk Factors for Invasive Aspergillosis in Patients with Acute Leukemia at Srinagarind Hospital, Khon Kaen University

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***Objective:*** Invasive aspergillosis (IA) is the most common fungal infection in patients with acute leukemia and associated with high mortality rate. We aimed to report the prevalence and clinical risk factors of IA in patients with acute leukemia at Srinagarind Hospital, Khon Kaen University.

***Materials and Methods:*** A retrospectively study was performed in adult acute leukemia patients who were diagnosed with IA from January 2006 to December 2015 at Srinagarind Hospital, Khon Kaen University. IA was defined by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group. Clinical characteristics and laboratory data were analyzed. Multivariate logistic regression analysis was used to determine the associations.

***Results:*** A total of 355 patients with acute leukemia, invasive aspergillosis was found in 39 patients (11%). The median age was 46 years (IQR of 33 to 59 years). Gender distribution was equal between males and females. Most common type of leukemias in the study are acute myeloid leukemia non-M3 (50.7%), followed by acute myeloid leukemia M3 (24.8%), and acute lymphoblastic leukemia (24.8%) respectively. Using logistic regression analysis, patients who had neutropenia at the time of IA diagnosed (adjusted OR 3.54; p=0.014), hepatitis B viral infection (adjusted OR 3.13; p=0.03), and working as construction worker (adjusted OR 23.08; p<0.001) remained the risk factor of IA.

***Conclusion:*** The prevalence of IA in Thai patients with acute leukemia is modest. Neutropenia, hepatitis B viral infection and construction worker were significant clinical risk factors for IA in patients with acute leukemia.

***Keywords:*** Invasive aspergillosis; Acute leukemia; Srinagarind Hospital

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Invasive aspergillosis (IA), an infection caused by filamentous fungi in the genus *Aspergillus*, is a major complication which is commonly seen in the patients with hematologic malignancies. From previous reports, the incidence of IA ranges from 5 to 24% in patients with acute leukemia, and 3 to 11% in patients who underwent allogeneic hematopoietic stem cell transplantation. Furthermore, the case fatality rate is more than 50% in patients with hematologic malignancies and reaches to 90% in those with allogeneic stem cell transplantation[1].

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The important risk factors for IA in patients with hematologic malignancies are prolonged duration of neutropenic episode, administration of steroids, type of chemotherapy, and type of malignancies, especially acute lymphatic leukemia, acute myeloid leukemia, and myelodysplastic syndrome[2]. At present, novel antifungal agents were developed for the purpose of IA prevention and treatment, however the incidence and mortality rate of patients in this group are still high[3].

In Thailand, estimated prevalence of IA using the LIFE program (www.LIFE-worldwide.org) is 13.5% in leukemic patients[4]. Established risk factors are neutropenia, chemotherapy, and receiving corticosteroid therapy which are comparable to worldwide studies[5]. Poorly controlled diabetes and history of pulmonary tuberculosis are also mentioned[6]. However, information on prevalence and risk factors for IA in patients with acute leukemia in Thailand are mostly reported form capital while data from regional remains limited, especially in the Northeast of Thailand, where high burdens of hematologic malignancies are reported. Early diagnosis and treatment may reduce the mortality rate in these patients. Therefore, this study is aimed to determine the prevalence and clinical risk factors of IA in patients with acute leukemia.

## Materials and Methods

A retrospective study was performed in adult patients aged ≥18 years old with acute leukemia diagnosed at Srinagarind Hospital, Khon Kaen University (Thailand) from January 2006 to December 2015. Medical records of patients with acute leukemia and IA were thoroughly reviewed. Data collected included baseline patient's characteristics, type of acute leukemia, chemotherapy protocols, phase of chemotherapy, neutropenia, previous episode of neutropenia, corticosteroid used, prior clinical history of proven or probable mold disease, site of infection, diagnosis invasive aspergillosis, and treatment outcomes. Patients were excluded if their medical records were incomplete.

### *Operational definitions*

#### *Invasive aspergillosis (IA)*

Invasive aspergillosis (IA) is diagnosed by criteria according to the definitions established by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) of the National Institute of Allergy and Infectious Disease[7].

The brief lists of diagnostic criteria are:

1) Proven IA is defined as an isolation of *Aspergillus* spp. from a normally sterile site obtained by a sterile procedure (from needle aspiration or biopsy specimen) or identification of typical hyphal elements compatible with *Aspergillus* spp. with evidence of associated tissue damage from histopathological or cytological report and clinically or radiologically abnormal site consistent with infection.

2) Probable IA is defined as the presence of at least one of host factor criterion as defined by the EORTC/MSG and the presence of positive culture results or cytological evidence or direct microscopic evaluation for *Aspergillus* spp. (microbiological criteria), and one major (or two minor) clinical criteria defined by the EORTC/MSG definitions.

3) Possible IA is defined by the presence of one microbiological criterion or one major (or two minor) clinical criterion in the appropriate host setting.

#### *Corticosteroid treatment*

Use of systemic corticosteroids at a therapeutic dose of ≥0.3 mg/kg of prednisolone or equivalent dose for ≥3 weeks in the past 60 days[7].

### *Sample size calculation*

Sample size calculation was based on primary objective of this study, which was to ascertain the estimated prevalence of IA in patients with acute leukemia. An estimated prevalence of 5 to 24% (17%) was derived from existing studies[8]. A formula for estimating a population proportion with specified absolute precision was used to calculate this. It was determined that a sample size of at least 342 participants.

### *Statistical analysis*

Continuous variables were presented as the median with interquartile range (IQR) or mean with standard deviation (SD), depending on they were in normal distribution or not. Categorical variables were reported as the number and percentage. Associations were expressed as odd ratio (OR) and 95% confidence interval (95% CI). The clinical risk factors of IA were analyzed using the univariate and the statistically significant factors (a probability value of <0.05) were selected for multivariate logistic regression method. All statistical analyses were performed using STATA program version 10 (StataCorp., College Station, TX, USA).

### *Ethical consideration*

Ethical approval was provided by the Ethics Committee of the Faculty of Medicine, Khon Kaen University according to the Declaration of Helsinki (Number HE591139).

## Results

A total of 355 participants were identified from database in our final analyses. non-M3 AML was the most common type of leukemia (158 patients, 50.7%) followed by AML M3 (82 patients, 24.8%) and ALL (76 patients, 24.5%). Gender distribution was equal between males and females. The median age was 46 years (33 to 59). Of 355 patients with acute leukemia, 39 patients (11%) were diagnosed as IA which 10 patients (25.6%) were classified to be proven IA, 22 (56.3%) were probable, and 7 (17.9%) were possible respectively. The most common sites of IA were lungs (30 patients, 78.9%), followed by sinuses (8 patients, 20.4%), and eyes (2 patients, 5.3%). Baseline characteristics of subjects with and without IA were shown in Table 1.

### *Factors associated IA in acute leukemia patients*

The univariate analysis of clinical risk factors for IA was shown in Table 2. IA was significantly found in patients with neutropenia at the time of diagnosis more than non-neutropenic patients (OR 6.39, 95% CI 3.15 to 12.96; p<0.001). In addition, acute leukemia patients who had increasing duration of neutropenic period for one day were associated with higher risk of IA development (OR 1.03, 95% CI 1.01 to 1.06; p=0.01).

For patient factors, working as a construction worker was significantly associated with IA in acute leukemia patients (OR 23.1, 95% CI 4.3 to 123.6; p<0.001). Furthermore, patients with hepatitis B viral infection had higher risk to develop IA compared to those without hepatitis B viral infection (OR 3.2, 95% CI 1.27 to 8.25; p=0.01).

The multivariate analyses of clinical risk factors for IA were shown in Table 3. After adjustment by multivariate logistic regression, three clinical risk factors were independently associated with IA in acute leukemia patients, including neutropenia (OR 3.54, 95% CI 1.28 to 9.73; p=0.014), hepatitis B viral infection (OR 3.13, 95% CI 1.11 to 8.84; p=0.03), and working as a construction worker (OR 23.08, 95% CI 3.58 to 140.6; p=0.001).

**Table 1.** Baseline characteristics of all 335-acute leukemia patients

| | Non-IA (n=316) | IA (n=39) | Total (n=355) |
|---|---|---|---|
| Female (%) | 158 (50) | 18 (46.2) | 176 (49.6) |
| Median age (years) (IQR) | 47 (32.5 to 39.5) | 44 (34.0 to 54.0) | 46 (33.0 to 59.0) |
| Occupation (%) | | | |
| Farmer | 124 (39.2) | 20 (51.3) | 144 (40.6) |
| Houseworker | 19 (6) | 2 (5.1) | 21 (5.9) |
| Office worker | 55 (17.4) | 3 (7.7) | 58 (16.3) |
| Freelancer&self-employed person | 62 (19.6) | 1 (2.6) | 63 (17.7) |
| Construction worker | 1 (0.3) | 3 (7.7) | 4 (1.1) |
| Mining worker | 1 (0.3) | 2 (5.1) | 3 (0.8) |
| Others[a] | 54 (17) | 11 (20.5) | 62 (17.5) |
| Underling disease (%) | | | |
| Diabetes mellitus | 31 (9.8) | 4 (10.3) | 35 (9.9) |
| Hypertension | 40 (12.7) | 3 (7.7) | 43 (12.1) |
| Chronic kidney disease | 16 (5.1) | 1 (2.6) | 17 (4.8) |
| Hepatitis B viral infection | 20 (6.3) | 7 (17.9) | 27 (7.6) |
| Others[b] | 48 (15) | 3 (7.8) | 51 (22.8) |
| Tobacco use (%) | 88 (27.8) | 10 (25.6) | 98 (27.6) |
| Alcohol use (%) | 102 (32.3) | 11 (28.2) | 113 (31.8) |
| Type of acute leukemia (%) | | | |
| Acute lymphoblastic leukemia | 76 (24.1) | 11 (28.2) | 87 (24.5) |
| Acute myeloid leukemia (non M3) | 158 (50) | 22 (56.4) | 180 (50.7) |
| Acute myeloid leukemia (M3) | 82 (25.9) | 6 (15.4) | 88 (24.8) |
| Corticosteroid treatment (%) | 42 (13.3) | 7 (17.9) | 49 (13.8) |
| Chemotherapy protocols[c] | | | |
| 7+3 regimen | 125 (39.6) | 18 (46.2) | 143 (40.3) |
| ATRA+idarubicin | 29 (9.2) | 5 (12.8) | 34 (10.2) |
| Hyper-CVAD | 10 (3.2) | 4 (10.3) | 14 (3.9) |
| ALL regimen | 53 (16.8) | 4 (10.3) | 57 (16.1) |
| COP regimen | 0 (0) | 1 (2.6) | 1 (0.3) |
| History of neutropenia | 69 (21.8) | 25 (64.1) | 94 (26.5) |
| Previous episodes of neutropenia | | | |
| 1 | 59 (18.7) | 6 (15.4) | 65 (18.3) |
| ≥2 | 11 (3.5) | 5 (12.8) | 16 (4.5) |

IA = invasive aspergilosis; IQR = inter quartile range; HSCT = hematologic stem cell transplanstation; ANC = absolute neutrophil count

[a] Others occupation were student, teacher, police, retirement, and monk

[b] Others underlying disease were myelodysplastic syndrome, solid malignancy, chronic obstructive pulmonary disease, asthma and metabolic syndrome

[c] Chemotherapy protocols: 7+3 regimen; cytarabine and Idarubicin, ATRA+idarubicin; arsenic trioxide plus idarubicin, Hyper-CVAD; course A: cyclophosphamide, vincristine, doxorubicin and dexamethasone, course B: methotrexate, and cytarabine. ALL regimen; induction with combinations of drugs, including vincristine, prednisone, cyclophosphamide, doxorubicin, and L-asparaginase, consolidation with cytarabine and methotrexate, Maintenance with 6-mercaptopurine, methotrexate, steroids, and vincristine, COP regimen; cyclophosphamide, vincristine, prednisone

[d] ANC at time of IA diagnosed

**Table 1.** Cont.

| | Non-IA (n=316) | IA (n=39) | Total (n=355) |
|---|---|---|---|
| ANC at time of diagnosis[d] (cells/mm$^3$) | | | |
| <100 | 28 (8.9) | 9 (23.1) | 37 (10.4) |
| 100 to 1,000 | 80 (25.3) | 21 (53.8) | 101 (28.5) |
| >1,000 | 208 (65.8) | 9 (23.1) | 217 (61.1) |
| Median duration of neutropenia (days) (IQR) | 20 (14 to 32) | 30 (18 to 60) | 25 (14 to 40) |
| Acute leukemic outcomes | | | |
| Complete response | 14 (4.4) | 5 (12.8) | 19 (5.4) |
| Partial response | 168 (53.2) | 5 (12.8) | 173 (48.7) |
| Failure | 19 (6) | 8 (20.5) | 27 (7.6) |
| Relapse | 0 (0) | 14 (35.9) | 14 (3.9) |
| Death | 27 (8.5) | 7 (17.9) | 34 (9.6) |
| Stable disease | 88 (27.8) | 0 (0) | 88 (24.8) |

IA = invasive aspergilosis; IQR = inter quartile range; HSCT = hematologic stem cell transplanstation; ANC = absolute neutrophil count

[a] Others occupation were student, teacher, police, retirement, and monk

[b] Others underlying disease were myelodysplastic syndrome, solid malignancy, chronic obstructive pulmonary disease, asthma and metabolic syndrome

[c] Chemotherapy protocols: 7+3 regimen; cytarabine and Idarubicin, ATRA+idarubicin; arsenic trioxide plus idarubicin, Hyper-CVAD; course A: cyclophosphamide, vincristine, doxorubicin and dexamethasone, course B: methotrexate, and cytarabine. ALL regimen; induction with combinations of drugs, including vincristine, prednisone, cyclophosphamide, doxorubicin, and L-asparaginase, consolidation with cytarabine and methotrexate, Maintenance with 6-mercaptopurine, methotrexate, steroids, and vincristine, COP regimen; cyclophosphamide, vincristine, prednisone

[d] ANC at time of IA diagnosed

## Discussion

In the patients with hematologic malignancies, neutropenia, anti-CD20 monoclonal antibody, immunosuppressive agent, and graft versus host disease are the established risk factors for emerging of pulmonary invasive fungal infection which are related to poorer outcomes and higher mortality rate[9]. Conversely, intensive chemotherapy and stem cell transplantation have improved the outcomes of the patients[10]. In our study, we retrospectively reviewed 355 patients with acute leukemia in a medical center from 2006 to 2016 and found the prevalence of IA in acute leukemia patients is 11% which is similar the previous studies that the prevalence percentage ranged from 5 to 50%[3,4,9,11,12]. We observed that patients with neutropenia, long duration of neutropenia, hepatitis B viral infection, and working as construction worker were correlated with developing of IA. After using multivariate logistic regression for adjustment, being neutropenia at the time of IA diagnosed, hepatitis B viral infection, and working as construction worker were remained the independent factors which associated with IA.

The authors found neutropenia at the time of IA diagnosed and prolonged duration of neutropenia were associated with IA. Although median duration of neutropenia in IA and non-IA group had no statistically significant, neutropenic period in IA group tended to be longer (30 vs. 20 days). Neutropenia and duration of neutropenia are substantial risk factors of infection including IA in hematologic malignancy and stem cell transplantation patients from others studies[2]. We hypothesized that impairment numerical (qualitative defects) and function (phagocytosis) circulating neutrophils causing IA.

This study also found that the patients who had an occupation as construction workers had a higher risk to develop IA. Construction activity has been reported that causing the outbreaks of invasive pulmonary aspergillosis in an ICU[13]. The infected patients are included two bone marrow transplanted recipients and one patient with AML. We assumed that *Aspergillosis* spp. usually lives in soil and organic debris, so the construction worker is more likely to get infected than any other occupations[13,14].

Hepatitis B viral infection is also an independent risk factor of IA from this study. Previous studies demonstrated the association between IA and acute-on-chronic liver disease which hepatitis B viral infection was the one of the causes[15,16]. Innate and adaptive cellular play an important role against *Aspergillus* spp. infection. We assumed those host defense mechanisms were impaired in acute leukemia patients with chronic liver disease.

This study has some limitations. First, there are

**Table 2.** Univariate logistic regression analysis of factors associated with IA in acute leukemia patients

| Factors | Unadjusted OR | 95% CI | p-value |
|---|---|---|---|
| Gender | 0.86 | 0.44 to 1.67 | 0.65 |
| Age | 1.00 | 0.98 to 1.02 | 0.85 |
| Construction worker | 23.09 | 4.31 to 123.58 | <0.001 |
| Underlying diseases | | | |
| Diabetes mellitus | 1.05 | 0.35 to 3.15 | 0.93 |
| Chronic kidney disease | 0.49 | 0.06 to 3.83 | 0.50 |
| Viral hepatitis B | 3.24 | 1.27 to 8.25 | 0.01 |
| Increasing neutropenic period for one day | 1.03 | 1.01 to 1.06 | 0.01 |
| Previous episode of neutropenia | 1.64 | 0.98 to 2.73 | 0.06 |
| Tobacco use | 0.89 | 0.42 to 1.91 | 0.77 |
| Family history of IA | 1.36 | 0.16 to 11.60 | 0.78 |
| Corticosteroid treatment | 1.43 | 0.59 to 3.44 | 0.43 |
| Type of leukemia | 0.74 | 0.46 to 1.20 | 0.22 |
| Chemotherapy regimen | 0.90 | 0.78 to 1.03 | 0.13 |
| Neutropenia at the time of diagnosis | 6.39 | 3.15 to 12.96 | <0.001 |
| ANC at the time of diagnosis (cells/$mm^3$) | | | |
| <100 | 7.43 | 2.72 to 20.29 | <0.001 |
| 100 to 1,000 | 6.07 | 2.67 to 13.81 | <0.001 |

OR = odds ratio; 95% CI = 95% confidence interval; IA = invasive aspergillosis; ANC = absolute neutrophil count

**Table 3.** Multiple logistic regression analysis of factors associated with IA in acute leukemia patients

| Factors | Adjusted OR | 95% CI | p-value |
|---|---|---|---|
| Neutropenia at time of diagnosis | 3.54 | 1.28 to 9.73 | 0.014 |
| COPD&asthma | 5.98 | 0.44 to 80.84 | 0.178 |
| Hepatitis B viral infection | 3.13 | 1.11 to 8.84 | 0.030 |
| Construction worker | 23.09 | 3.67 to 145.36 | <0.001 |
| Corticosteroid treatment | 0.69 | 0.25 to 1.91 | 0.488 |

OR = odds ratio; 95% CI = 95% confidence interval; COPD = chronic obstructive pulmonary disease

some missing data that we cannot obtain due to study design. Second, diagnosis of IA at Srinagarind Hospital in the past may be difficult due to limitation of facilities e.g., CT scan of the chest and turnaround time of serum galactomannan. Consequently, the overall prevalence of IA may be less than reality and the cases may be selected after galactomannan was available in the institute. Third, we have not evaluated other factors such as T lymphocytes and cytokine impairment in chronic liver disease which exhibit successful selection and clonal expansion of effector cells with activity against *Aspergillus* spp.[17]. However, our study has value for evaluating the risk factors of IA development in acute leukemia patients and the results could provide insights into giving patients better care and planning future studies.

In conclusion, neutropenia, hepatitis B viral infection and working as construction worker are associated with the clinical course of IA. The risk factors for IA should be recognized in order to prevention, prophylactic anti-fungal therapy, early diagnosis, and effective treatment.

## What is already known on this topic?

Incidence of IA in patients with acute leukemia ranges from 5 to 24%. Prolonged duration of neutropenic episode, administration of steroids, type of chemotherapy, and type of malignancies are important risk factors for IA.

## What this study adds?

Incidence of IA in patients with acute leukemia at

Srinagarind Hospital, Khon Kaen University is comparable to previous study. Hepatitis B viral infection and working as construction worker are associated with the clinical course of IA. These factors should be identified and corrected for IA prevention.

## Declarations

### *Consent for publication*

All of the authors consent to publication and grant the publisher exclusive license of the full copyright. Availability of data and material Data available on reasonable request.

### *Author's contributions*

SL collected the data and drafted the manuscript. AM and NT conceived and designed the study. AM, NT and WS read and commented on the manuscript. WS corrected the final version of manuscript.


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## Potential conflicts of interest

The authors declare no conflict of interest.

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