



Characteristics and risk factors for mortality of invasive non-*Aspergillus* mould infections in patients with haematologic diseases: A single-centre 7-year cohort study

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Summary

Since mould-active azole prophylaxis has become a standard approach for patients with high-risk haematologic diseases, the epidemiology of invasive fungal infections (IFIs) has shifted towards non-*Aspergillus* moulds. It was aimed to identify the epidemiology and characteristics of non-*Aspergillus* invasive mould infections (NAIMIs). Proven/probable NAIMIs developed in patients with haematologic diseases were reviewed from January 2011 to August 2018 at Catholic Hematology hospital, Seoul, Korea. There were 689 patients with proven/probable invasive mould infections; of them, 46 (47 isolates) were diagnosed with NAIMIs. Fungi of the Mucorales order ($n = 27$, 57.4%) were the most common causative fungi, followed by *Fusarium* ($n = 9$, 19.1%). Thirty-four patients (73.9%) had neutropenia upon diagnosis of NAIMIs, and 13 (28.3%) were allogeneic stem cell transplantation recipients. The most common site of NAIMIs was the lung ($n = 27$, 58.7%), followed by disseminated infections ($n = 8$, 17.4%). There were 23.9% ($n = 11$) breakthrough IFIs, and 73.9% ($n = 34$) had co-existing bacterial or viral infections. The overall mortality at 6 and 12 weeks was 30.4% and 39.1%, respectively. Breakthrough IFIs (adjusted hazards ratio [aHR] = 1.99, 95% CI: 1.3-4.41, $P = .031$) and surgical treatment (aHR = 0.09, 95% CI: 0.02-0.45, $P = .003$) were independently associated with 6-week overall mortality. NAIMIs were not rare and occur as a complex form of infection often accompanied by breakthrough/mixed/concurrent IFIs and bacterial or viral infections. More active diagnostic efforts for NAIMIs are needed.

KEYWORDS

azole, epidemiology, immunodeficiency, mucormycosis, non-*Aspergillus* moulds, prophylaxis, surgical treatment

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1 | INTRODUCTION

Invasive fungal infections (IFIs) remain a leading cause of morbidity and mortality in patients with haematologic diseases.¹ Antifungal prophylaxis has already been proven to be clinically effective in preventing IFIs in high-risk patients with haematologic diseases, and primary antifungal prophylaxis (PAP), particularly mould-active azole in high-risk groups is now a standard protocol in international guidelines.^{2,3} These recent advances in the use of PAP during chemotherapy and haematopoietic stem cell transplantation (HSCT) have reduced the number of IFIs and improved the survival of high-risk patients.^{4,5} However, they have also led to changes in the epidemiology of IFIs, and breakthrough IFIs that developed during treatment with mould-active azoles have been reported.⁶⁻⁹ Thus, concerns on increasing possibility of rare and more resistant mould infections have been raised,¹⁰ and recent reports have described increasing incidence of non-*Aspergillus* invasive mould infections (NAIMIs), often in patients receiving mould-active azole drugs.¹⁰⁻¹²

Clinically, it is difficult to distinguish NAIMIs from invasive aspergillosis (IA), and NAIMIs often have a progressive and aggressive course.¹⁰ NAIMIs should be distinguished from IA primarily because many of these non-*Aspergillus* moulds are not susceptible to or are intrinsically resistant to azoles, including voriconazole.¹³⁻¹⁵ This may lead to treatment failure and increased mortality. However, data for the epidemiology of NAIMIs are limited, owing to its rarity and the lack of microbiological confirmation.

This study aimed to identify the epidemiology, characteristics, and risk factors for mortality of NAIMIs in patients with haematologic diseases and to investigate whether the incidence of NAIMIs has increased since the introduction of PAP.

2 | PATIENTS AND METHOD

2.1 | Study design

We reviewed the medical records of all adult patients with haematologic diseases who were followed up at Catholic Hematology Hospital from January 2011 to August 2018 and identified all episodes of proven or probable NAIMIs (see "Definitions"). This tertiary hospital performs over 500 HSCTs annually. This study was conducted as part of Catholic Hematology Hospital Fungi Epidemiology (CAFÉ) study. Data including demographics, underlying diseases, main treatment of underlying haematologic diseases, administration of immunosuppressants and antibiotics, duration of neutropenia, severity of graft versus host disease (GVHD), co-existing bacterial or viral infection, antifungal and other therapies and clinical outcomes including 6-week and 12-week overall mortality.

During the study period, fluconazole was the main PAP agent in conventional chemotherapy for acute leukaemia from December 2010, while itraconazole syrup or micafungin was the PAP in allogeneic HSCT recipients. Both were administered prior to neutropenia (absolute neutrophil count $<500 \text{ mm}^{-3}$) until recovery. Posaconazole

was approved for PAP in remission induction chemotherapy for acute myeloid leukaemia (AML) and myelodysplastic syndrome in Korea since February 2013 and in patients with GVHD since July 2015. Secondary prophylaxis of voriconazole for patient with IA prior to allo-HSCT was approved in Korea in August 2015. Our centre has changed the PAP protocol accordingly.

The Institutional Review Board of Seoul St. Mary's Hospital (Approval number: KC18RESI0678) approved the research protocol and waived the need for informed consent owing to the retrospective nature of the study.

2.2 | Definitions

Definitions of proven/probable NAIMI were applied from the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions of IFIs.¹⁶ Disseminated IFI was defined as involvement of two or more non-contiguous sites or positive blood cultures.¹⁷ Past IFI was defined as a previous IFI over 2 weeks from the end of the treatment. Breakthrough IFI was defined as (1) occurrence of a proven/probable IFI according to EORTC/MSG definitions while on systemic mould-active agent PAP or within 14 days after discontinuation of PAP or (2) the appearance of any new lesions indicative of NAIMIs in a patient receiving systemic mould-active agent for at least 14 days with previously diagnosed IFI.^{9,11,17} Mixed IFI was defined as two or more fungal species identified in the same specimens,⁹ while concurrent IFI was defined as two different species identified in non-contiguous sites.

2.3 | Microbiologic methods

Moulds were identified primarily via phenotypic studies and morphology and biochemical analysis. Final identification of non-*Aspergillus* moulds was confirmed via sequencing of internal transcribed spacer (ITS). Their entire ITS regions were amplified using the primers of ITS1-F_KYO2 (5'-TAGAGGAAGTAAAAGTCGTAA-3') and ITS4 (5'-TCCTCCGCTATTGATATGC-3'), as previously described.¹⁸ ITS amplicons were sequenced, and then identified using the BLASTN (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>).

2.4 | Statistical analysis

Differences in qualitative variables between the patients with mucormycosis and those with other NAIMIs were analysed via χ^2 test with continuity correction or Fisher's exact test where appropriate. Meanwhile, differences in quantitative variables were compared via *t* test. To identify whether the incidence of NAIMIs has increased as year, Spearman correlation analysis was used. A Cox proportional hazards model was applied to identify the independent risk factors of 6-week mortality. A two-tailed *P* value of <0.05 was considered

significant. All statistical analyses were performed using SPSS software version 18.0 (SPSS Korea, Seoul, Korea).

3 | RESULTS

3.1 | Fungal isolates

There were 689 adult patients with proven or probable invasive mould infections (IMIs) during the study period, of which 46 patients (47 isolates; Figure 1) were diagnosed with proven or probable NAIMIs. Four cases out of 116 IMIs in 2011 (3.4%), 7 cases out of 77 IMIs in 2012 (9.0%), 5 cases out of 72 IMIs in 2013 (6.9%), 4 cases out of 99 IMIs in 2014 (4.0%), 3 cases out of 80 IMIs in 2015 (3.7%), 8 cases out of 99 IMIs in 2016 (8.0%), 8 cases out of 96 IMIs in 2017 (8.3%) and 7 cases out of 96 IMIs until August 2018 (14%) were NAIMIs (Figure 2). There was no significant increase in the proportion of NAIMIs in total IMIs from January 2011 to August 2018 (correlation coefficient [ρ] = 0.408, P = .364; Figure 2). In total, 28 cases (60.8%) met the proven criteria and 18 cases (39.1%) met the probable criteria (Table 1). Sixteen cases of NAIMIs were diagnosed via histopathology alone, and all these cases were mucormycosis (Figure 1). Meanwhile, four cases (8.7%) were diagnosed via combined culture and tissue histopathology. ITS sequencing was performed in 14 of 46 cases (30.4%).

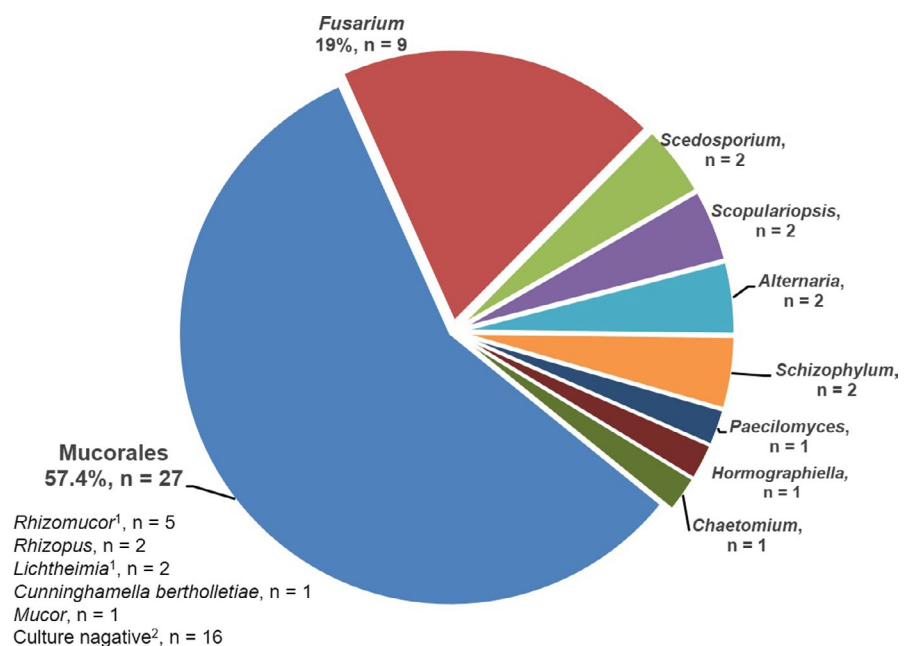
Mucorales (n = 27, 57.4%) was the most common causative fungi, followed by *Fusarium* (n = 9, 19.1%), *Alternaria* (n = 2), *Scopulariopsis* (n = 2), *Scedosporium* (n = 2), *Schizophyllum* (n = 2), *Paecilomyces* (n = 1), *Hormographiella* (n = 1) and *Chaetomium* (n = 1). One patient had mixed Mucorales; both *Rhizomucor* spp. and *Lichtheimia* spp. were identified in the same sinus tissue culture. Most Mucorales (16 of 27) were confirmed via histopathology alone due to negative culture, and *Rhizomucor* spp. (n = 5) was the most common species (Figure 1). Of the nine *Fusarium* isolates, three were *F solani*, while three others

were *F dimerum* (n = 1), *F fujikuroi* spp. complex (n = 1) and *F verticillioioides* (n = 1) confirmed via ITS sequencing, the remaining three isolates were unclassified. Of the two *Scedosporium*, one was *S prolificans*, while the other was *S aurantiacum*. Of the two *Scopulariopsis*, one was *S brevicaulis* and the other was unclassified. Two *Schizophyllum* were both *S commune* and two *Alternaria* species were unclassified. The genus *Paecilomyces* was *P variotii*; genus *Hormographiella*, *H aspergillata*; and genus *Chaetomium*, *C bostrychodes*.

3.2 | Patient characteristics, sites of infection and comorbidity

The characteristics of patients with NAIMIs are shown in Table 1. The median patient age was 52.3 years (\pm 11.2), and 69.6% (n = 32) of the patients were male. In total, 28.3% (n = 13) of NAIMIs occurred in patients with allo-HSCT, and 73.9% (n = 34) had neutropenia upon the diagnosis of NAIMI. There was no statistically significant difference in the rate of patients with neutropenia at the time of diagnosis between the mucormycosis group and other NAIMIs group, but the duration of prediagnosis neutropenia tended to be longer in the other NAIMIs group than that in the mucormycosis group (Table 2, P = .008). The incidence of proven category was higher in the mucormycosis group than that in the other NAIMIs group (80.8% vs 35.0%, P = .001), and this was due to the higher frequency of surgical treatment in the mucormycosis group. The most common site of NAIMI was the lung (58.7%, n = 27), followed by disseminated infections (17.4%, n = 8) and the sinus (10.9%, n = 5). Of the eight disseminated infections, six were fungemia (all *Fusarium* spp.), two were mucormycosis (one patient met the probable criteria of pulmonary mucormycosis and also met the proven category via skin histopathology, while the other met the proven criteria via surgery of the lung, liver and stomach).

FIGURE 1 Distribution of non-*Aspergillus* moulds causing invasive infections in patients with haematologic diseases. ¹Two species were identified simultaneously in one patient tissue culture. ²Diagnosed via pathology, but negative on culture



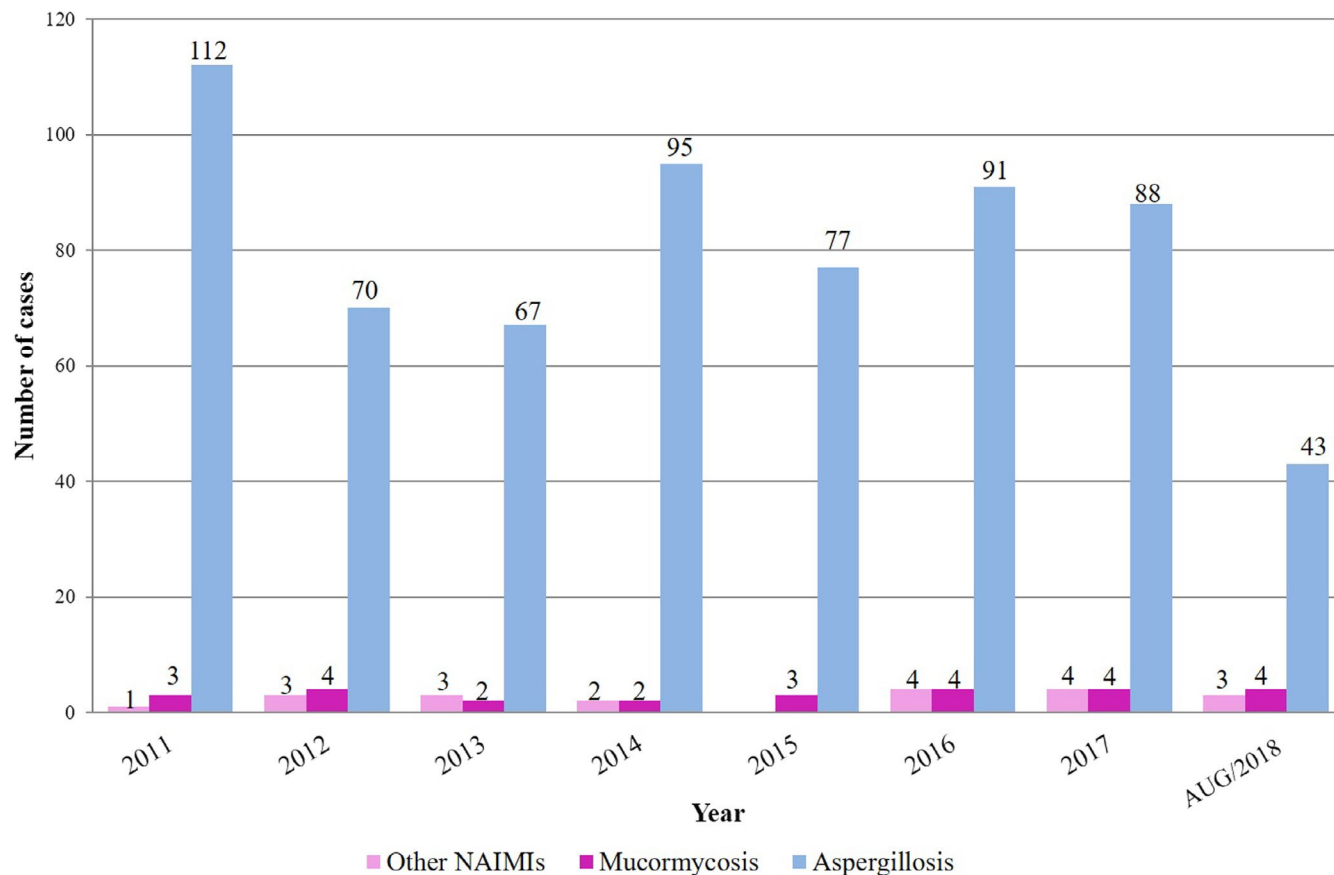


FIGURE 2 Proportion of non-*Aspergillus* invasive mould infections to total annual number of invasive mould infections. These bar charts show the number of non-*Aspergillus* invasive mould infections and *Aspergillus* infections in the corresponding year. There was no significant increase in the proportion of NAIMIs (correlation coefficient [ρ] = 0.408, P = .364) within the study period. NAIMI, non-*Aspergillus* mould infection

Three patients had past IFI, and all three had probable invasive pulmonary aspergillosis (IPA). In total, 11 cases (23.9%) of breakthrough IFIs occurred during the use of mould-active antifungal agents: five cases occurred during voriconazole treatment, and all cases were performed voriconazole therapeutic drug monitoring (TDM) every week. The appropriate therapeutic range of voriconazole (1.0–5.5 $\mu\text{g}/\text{mL}$) was maintained in four of the five patients. Meanwhile, in the other patient the dose was under the appropriate therapeutic range and was thus doubled to maintain the appropriate range (200mg bid, then 300mg bid and then 400mg bid). Further, 2 of 11 cases of breakthrough IFIs occurred during itraconazole treatment for possible category of IPA; meanwhile, another four cases occurred during posaconazole PAP, all of which were managed via TDM every week and the posaconazole dose was maintained in the appropriate therapeutic range (≥ 700 ng/mL). Ten cases of mixed IFI were noted, and all ten cases were IA (one of the ten met both the proven criteria of IA and mucormycosis). Seven cases of concurrent IFI were found; of these, four cases were IPA, one was IA proven via liver biopsy, one was IA proven via cerebrospinal fluid culture and one was chronic disseminated candidiasis in the liver. Thirty-four patients (73.9%) had co-existing bacterial or viral infections within 2 weeks after the diagnosis of NAIMI. The most common bacterial infection was *Escherichia coli* bacteraemia

(n = 7) followed by vancomycin-susceptible enterococcus bacteraemia (n = 5). The most common comorbid viral infection was cytomegalovirus (two cases were organ-involved diseases, five cases were DNAemia only). Overlapping infections were also common; for instance, one patient had mucormycosis co-occurring with methicillin-resistant coagulase-negative *Staphylococci* identified in the sinus tissue culture followed by carbapenem-resistant *Acinetobacter baumannii* bacteraemia, *E. coli* bacteraemia and *Stenotrophomonas maltophilia* bacteraemia within 2 weeks. There were 22 patients (47.8%) who had undergone surgical treatment, and majority had mucormycosis (Table 2, P < .001).

3.3 | Outcomes

The overall mortality at 6 and 12 weeks was 30.4% and 39.1%, respectively. Although there was no statistically significant difference in overall mortality between the mucormycosis group and the other NAIMIs group, 20 of the 26 mucormycosis patients who underwent surgery showed a survival rate of 90.0% at 6 weeks. Six patients died within 6 weeks; of these, 66.7% (4/6) died because they did not undergo surgical treatment due to progression of mucormycosis (mean duration of diagnosis to death = 13.3 days), and

TABLE 1 Characteristics of patients with non-*Aspergillus* mould infections

| Characteristics | |
|--|-----------------------|
| Age, median (range) y | 52.3 (22-77) |
| Males, no. (%) | 32 (69.6) |
| Underlying disease, no. (%) | |
| AML/2ndary AML | 21 (45.7) |
| ALL | 10 (21.7) |
| MDS | 5 (10.9) |
| AA | 3 (6.5) |
| Others | 7 ^a (15.2) |
| Treatment, no (%) | |
| Conventional chemotherapy ^b | 19 (41.3) |
| HSCT | 13 (28.3) |
| Other chemotherapy ^c | 3 (6.5) |
| Conservative care | 11 (23.9) |
| Neutropenia (ANC < 500/mm ³) | 34 (73.9) |
| Duration of neutropenia ^d , mean (SD) days | 33.2 (19.9) |
| Acute GVHD (grade ≥ II) or chronic extensive GVHD, no. (%) | 7 (15.2) |
| Baseline use of prednisolone (mg/kg/d), no. (%) | |
| >1.0 | 4 (8.7) |
| ≤1.0 but ≥ 0.4 | 2 (4.3) |
| No. of other immunosuppressive agents, no. (%) | |
| 1 | 7 (15.2) |
| ≥2 | 6 (13.0) |
| IFI category, no. (%) | |
| Probable | 18 (39.1) |
| Proven | 28 (60.8) |
| Site of IFI, no. (%) | |
| Lung | 27 (58.7) |
| Sinus | 5 (10.9) |
| Disseminated | 8 (17.4) |
| Other sites | 6 (13.0) |
| Past IFI, no. (%) | |
| Breakthrough IFI, no. (%) | 11 (23.9) |
| Mixed IFI, no. (%) | 5 (19.2) |
| Concurrent IFI, no. (%) | 4 (15.4) |
| Co-existing infection other than IFI, no. (%) | 15 (57.7) |
| Surgical treatment | |
| Overall mortality at 6-wk | 14 (30.4) |
| Overall mortality at 12-wk | 19 (39.1) |

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation; IFI, invasive fungal infection; MDS, myelodysplastic syndrome; NAIMI, non-*Aspergillus* invasive mold infection.

^aMultiple myeloma (n = 1), Primary myelofibrosis (n = 1), Diffuse large B cell lymphoma (n = 2), Hemophagocytic lymphohistiocytosis (n = 1), Chronic myeloid leukemia (n = 2).

^bRemission induction and consolidation and re-induction chemotherapy for acute leukemia and MDS.

^cOther chemotherapy: Two patients were undergoing decitabine chemotherapy, one patient received rituximab plus etoposide treatment.

^dWithin 60 d prior to NAIMI.

50.0% (3/6) had breakthrough IFIs. The major cause of death in the two cases who underwent surgery was not mucormycosis; one died from bacteraemia and the other from tumour lysis syndrome. Meanwhile, NAIMI was not the major cause of death in 75% (6/8) of patients in the other NAIMIs group; four cases died from bacteraemia, two died from progression of underlying haematologic diseases. In total, 25% (2/8) of patients who died in the other NAIMIs group were breakthrough IFI. Except both *F solani* fungemia and *S prolificans* bone and joint infection who underwent surgery, the clinical features of the patients who died within 6 weeks (mean duration of diagnosis to death = 8.3 days) that made them unsuitable for surgical treatment were similar to those in the mucormycosis group.

In multivariate analysis, breakthrough IFI (45.5% (5/11) vs 26.5% (9/34), aHR = 1.99, 95% CI: 1.3-4.41, *P* = .031) and surgical treatment (13.6% (3/22) vs 45.8% (11/24), aHR = 0.09, 95% CI: 0.02-0.45, *P* = .003) were independently associated with 6-week overall mortality in patients with haematologic diseases who developed NAIMIs.

4 | DISCUSSION

This cohort study showed the current trend in the epidemiology of NAIMIs before and after the introduction of mould-active azole PAP at a single centre in Korea. NAIMIs accounted for 6.7% of the total IMIs in patients with haematologic diseases during the study period. The causative fungi of NAIMIs in the patients with haematologic diseases varied. Similar to the findings in other studies, Mucorales was the most common cause of NAIMIs followed by *Fusarium* spp.^{10,12,17} The proportion of NAIMIs in total IMIs did not increase significantly within the study period, but in 2018, seven cases (four of seven are mucormycosis) were already recorded by August, and we expect that the incidence will exceed that in the previous year (Figure 2). Therefore, the trend in incidence should be monitored over the next few years to determine whether the incidence of NAIMIs did increase after the introduction of mould-active azole prophylaxis in Korea.

The overall all-cause mortality at 12 weeks was 39.1%, and this was lower than previously reports.^{13,16,17,19} There was no significant difference in overall mortality at 6 and 12 weeks between the mucormycosis group and the other NAIMIs group in this study, but the duration of neutropenia before diagnosis more likely longer in the other NAIMIs group. And co-existing infection other than IFIs was more in the other NAIMIs group than mucormycosis group (Table 2). Although not statistically significant in the multivariate analysis, these factors could be considered as one of reasons for the considerable low rate of surgical treatment in the other NAIMIs group.

Similar to other studies,^{17,20,21} surgical treatment was an independent predictor of good outcome within 6 weeks on multivariate analysis (aHR = 0.09, 95% CI: 0.02-0.45, *P* = .003). Surgical treatment of NAIMIs was performed actively in most cases except for those who developed progression of underlying haematologic diseases or

| Characteristics | Mucormycosis (n = 26) | Other NAIMIs (n = 20) | P value |
|---|--------------------------|--------------------------|---------|
| Age, median (range) y | 50.0 (23-77) | 55.4 (22-73) | .195 |
| Neutropenia (ANC < 500/mm ³) | 21 (80.8) | 13 (65.0) | .227 |
| Duration of neutropenia ^a , mean (SD) d | 14.6 (6.7) | 25.7 (11.7) | .008 |
| IFI category, no. (%) | | | |
| Probable | 5 (19.2) | 13 (65.0) | .001 |
| Proven | 21 (80.8) | 7 (35.0) | |
| Site of IFI, no. (%) | | | |
| Lung | 17 (65.4) | 10 (50.0) | .155 |
| Sinus | 3 (11.5) | 2 (10.0) | |
| Disseminated | 2 (7.7) | 6 (30.0) | |
| Other sites | 4 (15.4) | 2 (10.0) | |
| Past IFI, no. (%) | 2 (7.7) | 1 (20.0) | .732 |
| Breakthrough IFI, No. (%) | | | |
| Voriconazole ^b | 3 | 2 | |
| Posaconazole PAP ^c | 2 | 2 | |
| Itraconazole ^d | 1 | 1 | |
| Mixed IFI, no. (%) | 5 (19.2) | 5 (25.0) | .726 |
| Concurrent IFI, no. (%) | 4 (15.4) | 3 (15.0) | .713 |
| Co-existing infection other than IFI, no. (%) | 15 (57.7) | 19 (95.0) | .004 |
| Surgical treatment | 20 (76.9) | 2 (10.0) | <.001 |
| Overall mortality at 6-wk | 6 (23.1) | 8 (40.0) | .216 |
| Overall mortality at 12-wk | 7 (26.9) | 11 (55.5) | .136 |

Abbreviations: IFI, invasive fungal infection; NAIMI, non-*Aspergillus* invasive mould infection; PAP, primary antifungal prophylaxis.

^aWithin 60 d prior to NAIMI.

^bAll five cases were occurred during the treatment of probable IPA. The mean duration of voriconazole exposure was 69 d.

^cThe mean duration of posaconazole PAP exposure was 35.3 d.

^dAll two cases were occurred during the treatment of possible category of IPA. the mean duration of itraconazole exposure was 57.5 d.

co-existing bacteraemia and those who had fungemia alone that did not require surgery. In this study, majority of mucormycosis patients (76.9%) underwent surgery, in other words, most of mucormycosis patients were eligible for surgery which is associated with a favourable outcome at the time of diagnosis. Particularly, the overall 12-week mortality of mucormycosis patients who underwent surgical treatment was 15%, which is lower than that previously reported as 25%-50%.²⁰ Therefore, when it is suspected mucormycosis, early aggressive surgical treatment should be performed as soon as possible to reduce mortality.

Another key finding was that NAIMIs are not only single infection; rather, complex forms of infections should be considered. Ten patients (21.7%) had mixed IFIs, seven patients (15.2%) had concurrent IFIs and 11 patients had breakthrough IFIs (23.9%). Of these, breakthrough IFI is well-known risk factor for mortality in remission induction chemotherapy of AML patients and allo-HSCT

TABLE 2 Comparison of features of patients with mucormycosis and other non-*Aspergillus* mould infections

recipients.^{6-9,11,12,17,19} Similarly, multivariate analysis in our study showed that breakthrough IFI is an independent predictor of poor outcome (aHR = 1.99, 95% CI: 1.3-4.41, *P* = .031).

There is no distinct clinical finding, including radiologic and biomarker test, that could differentiate IA from NAIMI.²² Furthermore, several patients (73.9%) also have co-existing bacterial or viral infections, making accurate diagnosis more difficult. Therefore, diagnosis may require invasive procedures such as bronchoscopy or even surgery for tissue biopsy and culture; however, it is difficult to perform due to the poor general condition of the patients. In these cases, a worsening clinical course despite treatment is the only sign for NAIMIs.

This study had some limitations. First, this was a retrospective study performed at a single centre. Second, sequencing methods to accurately identify the moulds were not conducted in all cases because some were not grow in culture and were thus diagnosed

via histopathology alone. The histopathological results alone are not reliable for distinguishing IA from NAIMI. So we have a histopathological result after surgery, infectious diseases specialists, haematologists, radiologist of the chest and pathologist of lung come together to perform an exclusive diagnosis pathway considering the clinical situations of the patient. Combine the underlying disease of the patient, recent treatments (especially IFI therapy), new imaging findings and laboratory findings (GM negative, persistent neutropenia state, etc), decide whether to treat with NAIMI or IA. The NAIMIs in our data were diagnosed with through the above-mentioned exclusively diagnostic process and included only when treated NAIMI. But nevertheless, the rate of rare moulds could have been underestimated. Third, some cases did not grow in culture, and thus the antifungal susceptibility test could not be performed in all cases. Fourth, despite of the repetitive efforts to obtain adequate specimens, only specimens with low reliability, such as sputum, were obtained in some patients. These cases were categorised as the probable classification after correlating the host immune status and imaging findings from the EORTC/MSG definitions.

Despite these limitations, this study shows that epidemiology of NAIMIs is not limited to PAP in high-risk patients with haematologic diseases but also shows that NAIMIs were not rare in the clinical setting. Surgical treatment, particularly in suspected cases of mucormycosis, was associated with a significant survival benefit. Mortality remained high, especially in breakthrough cases. Attentive diagnostic efforts are crucial given the high rate of breakthrough, mixed, and concurrent IFIs and co-existing bacterial or viral infections. Further long-term investigations are needed to confirm whether the incidence of NAIMIs increased since the introduction of the mould-active azole PAP era.

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CONFLICT OF INTERESTS

DG Lee has served as a consultant and a board member for Astellas, Gilead, MSD, Pfizer and Yuhan and has received research support, travel support and payment for lectures, including service on speaker's bureaus, from Astellas, Gilead, MSD, Pfizer and Yuhan. The other authors declare no conflict of interests.

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