Journal of Infection and Public Health 16 (2023) 2001–2009

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: www.elsevier.com/locate/jiph

Original article

Characteristics and outcomes for pulmonary aspergillosis in critically ill patients without influenza: A 3-year retrospective study

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ARTICLE INFO

Article history:
Received 5 April 2023
Received in revised form 15 September 2023
Accepted 25 September 2023

Keywords:
Antifungal therapy
Aspergillosis
Intensive care unit
Mortality
Outcome

ABSTRACT

Background: Previous studies have revealed higher mortality rates in patients of severe influenza coinfected with invasive pulmonary aspergillosis (IPA) than in those without the coinfection; nonetheless, the clinical outcome of IPA in critically ill patients without influenza remains unclear.
Patients and methods: This retrospective study was conducted in three institutes. From 2016–2018, all adult patients diagnosed with IPA in the intensive care units (ICUs) were identified. The logistic regression was used to identify the potential risk factors associated with in-hospital mortality in patients with non-influenza IPA. The stratified analysis of IPA patients with and without antifungal therapy was also performed. The final model was established using a forward approach, selecting variables with p-values less than 0.05.
Results: Ninety patients were included during the study period, and 63 (70%) were men. The most common comorbidity was diabetes mellitus (n = 24, 27%), followed by solid cancers (n = 22, 24%). Antifungal therapy was administered to 50 (56%) patients, mostly voriconazole (n = 44). The in-hospital mortality rate was 49% (n = 44). Univariate analysis revealed that the risk factors for mortality included daily steroid dose, APACHE II score, SOFA score, C-reactive protein (CRP) level, carbapenem use, antifungal therapy, and caspofungin use. Multiple regression analysis identified four independent risk factors for mortality: age (Odds ratio [OR], 1.052, p = 0.013), daily steroid dose (OR, 1.057, p = 0.002), APACHE II score (OR, 1.094, p = 0.012), and CRP level (OR, 1.007, p = 0.008). Furthermore, the multivariable analysis identified that more physicians would initiate antifungal therapy for patients with prolonged steroid use (p = 0.001), lower white blood cell count (p = 0.021), and higher SOFA score (p = 0.048). Thus, under the selection bias, the independent risk factors for mortality in the antifungal treatment subgroup were daily steroid dose (OR, 1.046, p = 0.001) and CRP (OR, 1.006, p = 0.018), whereas the independent risk factor for mortality in the untreated group became APACHE II score (OR, 1.232, p = 0.007).
Conclusions: Patients with IPA had a substantially high mortality. Overall, age, steroid use, APACHE II score, and CRP level were identified as the independent risk factors for mortality in patients in the ICU.

Introduction

Aspergillus is a mold that is ubiquitous in the environment. Although people can acquire *Aspergillus* through inhalation of its spores, it rarely causes diseases in a normal human host [1,2].

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https://doi.org/10.1016/j.jiph.2023.09.016

Aspergillus lung disease is a wide spectrum of clinical syndromes, including allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis, and invasive pulmonary aspergillosis (IPA), which is determined by the immune status and pulmonary condition of the host [1,2]. Traditionally, IPA occurs in severely immunocompromised or neutropenic patients. However, an increasing number of IPA cases have been reported in non-neutropenic, critically ill patients [3–8]. The risk factors of IPA in critically ill patients without severe immunocompromised conditions include the use of corticosteroids, chronic lung disease, liver cirrhosis, and multiple organ dysfunction [1,2]. Most importantly, IPA may be associated with high morbidity and mortality [5,9,10]. Therefore, IPA in critically ill patients has become a serious concern in intensive care units (ICU). Recently, many studies have reported an association between influenza and IPA [3,11,12]. However, the outcomes of patients with IPA without influenza in ICUs remain unclear. The indication for antifungal therapy and the risk factors contributing to the mortality of IPA in critically ill patients remain unidentified in Taiwan. Therefore, we conducted a 3-year multi-center study to clarify the clinical characteristics of patients with IPA but without influenza staying in ICUs in Taiwan. We retrospectively adopted the recently updated definitions to evaluate the outcome of the IPA patients in real-world clinical practice.

Methods

Study design

This retrospective study was conducted in three hospitals: one medical center, one regional hospital, and one district hospital in southern Taiwan. From 2016–2018, all adult patients with IPA admitted to the ICU were identified, and only the first episode of IPA-related ICU admission was included. To exclude the impact of influenza, we only included patients who did not have concomitant influenza, which was defined as the patients who had negative results for rapid influenza diagnostic tests and/or real-time polymerase chain reaction of influenza A, influenza B, influenza A (H1N1), and influenza A (H3N2) during the same episode of hospitalization [13]. We recorded their clinical data, including sex, age, underlying diseases, recent use of corticosteroids, radiographic findings, initial laboratory data, disease severity using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score at ICU admission, acute respiratory distress syndrome (ARDS), sequential organ failure assessment (SOFA) scores, antifungal treatment, and organ support. In addition, the results of the laboratory examinations were obtained from the electronic health records of Chi Mei Medical Systems. The APACHE II score has been widely used as a severity classification system to predict outcomes in critically ill patients based on 12 objective physiological measurements, age, and chronic health conditions [14]. The SOFA is another severity-of-disease scoring system used to evaluate the extent of organ dysfunction in critically ill patients, measuring dysfunction in six key organ systems [15]. ARDS was defined according to the Berlin definition using the arterial oxygen tension (PaO2)/ the inspired oxygen fraction (FiO2) oxygenation criteria (mild, PaO2/FiO2 ≤ 300 mmHg; moderate, PaO2/FiO2 ≤ 200 mmHg; or severe, PaO2/FiO2 ≤ 100 mmHg) [16]. The primary outcome was all-cause in-hospital mortality of the episode.

Definition

In this study, we presumed ICU admission of adults with classically immunocompromised status (including glucocorticoid treatment with prednisone equivalent of 20 mg or more per day, hematological malignancies, solid organ transplantation recipient, and human immunodeficiency virus infection) or modified immunocompromised medical disorders (including diabetes mellitus, chronic obstructive lung disease, bronchiectasis, liver cirrhosis, end-stage renal disease, autoimmune disorders, and solid cancers) to be a host factor for acquiring IPA [17].

We intended to include proven or probable IPA cases. Proven IPA was defined as the presence of histological evidence of branching hyphae seen on lung biopsy. Probable IPA was generally based on the presence of clinical symptoms of pneumonia and imaging features of a halo sign, air crescent sign, cavity, wedge-shaped or necrotizing consolidation, nodular patchy, or acute alveolar infiltrates in the lungs with mycological evidence of either (1) cytology, direct microscopy, and/or culture indicating the presence of *Aspergillus* spp. in a lower respiratory tract specimen or (2) positive galactomannan (GM) antigen in the serum and/or bronchoalveolar lavage (BAL) fluid [18,19].

According to recently revised and updated consensus definitions applicable in the ICU setting in 2021 [18], positive *Aspergillus* GM antigen was defined as GM antigen optical density index > 0.5 in plasma/serum and/or GM antigen > 0.8 in BAL fluid. However, Zhou et al. [19]. reported that the optimized diagnostic cutoff value of GM antigen index for pulmonary aspergillosis was 0.7 in BAL fluid for the cohort mainly in south China, which is geographically proximate to Taiwan. Therefore, for our ICU patients in Taiwan, we adapted ≥ 0.7 as the BAL GM cutoff value for IPA. The cutoff value for serum GM detection is generally set at 0.5 [18–20]. Thus, the included cases in the current study would have a GM antigen index ≥ 0.5 in serum and/or ≥ 0.7 in BAL fluid using Platelia *Aspergillus* Ag assay (Bio-Rad Laboratories, Marnes-La-Coquette, France). As retrospective nature, it happened that the attending physicians might not necessarily treat the included cases with antifungal agents. In addition, we defined bacterial coinfection as the identification of other respiratory isolates within 2 days of IPA diagnosis, as previously described [21].

Statistical analysis

The clinical characteristics of the two groups were compared using the $\chi 2$ test or Fisher's exact test for categorical variables. The Mann-Whitney U test was used to compare the differences in continuous variables between the two independent groups. After screening from Chi-square distribution and univariate analysis, we used multivariable logistic regression models to identify the factors that are independently associated with in-hospital mortality, as well as the factors that are associated with receiving antifungal therapy (implying patient-selection bias by attending physicians). The odds ratios (OR) with 95% confidence intervals (CI) and *p*-values for these associations are reported. The stratified analysis of IPA patients with and without antifungal therapy was also performed as therapeutic bias in patient selection potentially confounding the mortality risks. We presented all significant univariate variables and potential risk variables in the initial full model. The final model was established using a forward approach, selecting variables with *p*-values less than 0.05. A two-tailed *p*-value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 18.

Results

Study subjects

During the three-year period, 237 patients with probable IPA were identified. After excluding 40 patients with confirmed concomitant influenza and 107 who did not undergo testing for any influenza assay, 90 patients who tested negative for influenza were included in the study. Among the study cohort, 64 (71.1%) patients were from a medical center, 25 (27.8%) were from a regional hospital,

Table 1
Distribution of case number and mortality for the stratified galactomannan (GM) antigen levels in the 31 BAL and 85 serum samples from 90 included positive cohorts (26 patients underwent both BAL and serum GM testing, 4 of which showed both positive results).

BAL (n = 31)	Number of patients	Mortality	%	P
Negative (< 0.7)[a]	9	4	44.4	0.457 ($P1$)
Positive				
0.7–0.8	0	0	0	
0.8–0.9	2	0	0	
> 0.9–1	2	0	0	
> 1–3	8	8	100	
> 3–5	2	2	100	
> 5	8	3	37.5	
Subtotal	22 (71.0%)	13	59	NA ($P3$)
Serum (n = 85)	Number of patients	Mortality	%	P
Negative (< 0.5)[b]	13	7	53.8	0.660 ($P2$)
Positive				
0.5–0.6	9	4	44.4	
> 0.6–1	22	9	40.9	
> 1–2	24	10	41.7	
> 2–4	9	7	77.8	
> 4	8	4	50	
Subtotal	72 (84.7%)	34	47.2	0.396 ($P3$)

Note. [a] Positive for serum samples; [b] Positive for BAL samples; BAL, bronchoalveolar lavage; NA: not available (as zero of the variables); $P1$, comparison of mortality rates between BAL-negative and -positive groups; $P2$, comparison of mortality between serum-negative and -positive groups; $P3$, comparison of mortality rates among the stratified GM levels within the BAL- or serum-positive subgroup.

and only one (1.1%) was from a district hospital in the same city in southern Taiwan.

All 90 patients were classified as probable IPA. *Aspergillus* spp. was isolated in only four (4.4%) patients. A total of 31 patients underwent GM testing in the BAL, while 85 patients underwent GM testing using blood samples (Table 1). The specimens that tested positive for GM in the study group included the BAL (n = 22; mean index, 3.56; standard deviation, 2.56; range, 0.80–8.61), blood samples (n = 72, mean index, 1.82; standard deviation, 1.74; range, 0.50–7.84), and both BAL and blood samples (n = 4). There were no GM data ranging from 0.7 to 0.8 in the BAL-positive samples. In addition, GM-positive patients had significantly higher mean GM index values in the BAL specimens than in the blood samples (p = 0.0012).

The distribution of BAL and serum GM index levels among the 90 IPA patients are stratified in Table 1, which indicates the non-significant differences in mortality rates between GM-positive and GM-negative groups either in the BAL (p = 0.457) or in the serum samples (p = 0.660) as well as among the stratified GM index levels within the serum-positive group (p = 0.396).

Clinical characteristics of patients with IPA (Table 2)

The mean age of the 90 patients with IPA was 65.3 years and 63 (70%) patients were men. The most common underlying disorder was diabetes mellitus (n = 24, 26.7%), followed by solid cancers (n = 22, 24.4%), including nasopharyngeal cancer (n = 6), head and neck cancer (n = 4), and lung cancer (n = 4). Traditional immunocompromised conditions were mainly glucocorticoid treatment for at least 5 days before acquiring IPA (n = 64, 71.1%), nonetheless, others were uncommon, such as hematological malignancy (n = 6, 6.7%), solid organ transplantation (n = 5, 5.6%), and human immunodeficiency virus infection (n = 1, 1.1%). The mean Charlson comorbidity index was 4.9. The disease severity status was 20.6 and 7.5 for the mean APACHE II and SOFA scores, respectively. Among them, 83 (92.2%) had septic shock and 61 (67.8%) had ARDS. 73.8% (45/61) of ARDS were of mild-to-moderate severity. Acute respiratory failure occurred in 53 (58.9%) patients who required invasive mechanical ventilation (MV) and four (4.4%) who required extracorporeal membrane oxygenation (ECMO) for organ support. Community-acquired pneumonia occurred in 81 (90%) patients. The most common radiological features were multiple patches with necrotizing processes (n = 22, 24.4%) followed by extensive consolidation on unilateral lung (n = 18, 20%), patch infiltrates in bilateral lungs (n = 16, 17.8%), and peribronchial infiltrations (n = 12, 13.3%). 55.6% (50/90) of IPA patients did not have extensive lung involvement.

Regarding the status of co-infection, 26 (28.9%) patients had concurrent respiratory bacterial isolates and 21 (23.3%) developed bacterial bloodstream infections. Carbapenems were administered to 25 (27.8%) patients. Antifungal therapy was administered to 50 (55.6%) patients, mostly voriconazole (n = 44), which might follow empirical therapy with caspofungin or subsequently be switched to or co-administered with liposomal amphotericin B or anidulafungin. Regarding clinical outcomes, 24 (26.7%) patients required prolonged ICU stay (≥ 21 days), the mean hospitalization duration was 31 days, and the overall in-hospital mortality was 48.9% (n = 44).

Difference in the patients with IPA that survived or died (Table 2)

We found that patients with mortality received higher daily doses of steroids and had higher disease severity (both APACHE II and SOFA scores) and higher C-reactive protein (CRP) levels than the survival group (all p < 0.05). In addition, the mortality group had more frequently received carbapenem therapy (p = 0.024) and antifungal therapy (p = 0.018), particularly with caspofungin (p = 0.015), than the survival group. Finally, the mortality group had significantly higher hospital costs than the survival group (p = 0.032), mainly because of drug fees (p = 0.018).

In contrast, no significant difference was found between the mortality and survival groups in the distribution of hospital, age (p = 0.05), sex, specific underlying disease or Charlson comorbidity score, use of MV or ECMO, presence of septic shock, radiographic findings, the severity of ARDS, laboratory findings other than CRP, bloodstream and respiratory co-bacterial infections, GM test day and its relevant data, and duration of hospital stay (all p > 0.05)..

Overall analysis: The risk factors predicting mortality of patients with IPA (Table 3)

Univariate analysis revealed that mortality was significantly associated with higher daily steroid dose, higher APACHE II score, higher SOFA score, higher CRP level, more carbapenem therapy, more antifungal therapy, and more caspofungin therapy. Further multivariable analysis using logistic regression for potential variables identified four predictors in the final forward approach model, including older age (OR = 1.052; 95% CI, 1.011–1.094; p = 0.013), higher daily steroid dose (OR = 1.057; 95% CI, 1.021–1.095; p = 0.002), higher APACHE II score (OR = 1.094; 95% CI, 1.020–1.174; p = 0.012), and higher CRP (OR = 1.007; 95% CI, 1.002–1.012; p = 0.008), which were independently significantly associated with increasing mortality among patients with IPA in the ICU. The apparently significant factors of more carbapenem therapy, more antifungal therapy, and more caspofungin therapy became non-significant in the multivariable analysis using either full model or final forward approach, indicating non-independent nature of these factors. For example, physicians would like to treat patients with carbapenem in the presence of severe disease such as high APACHE II score. Although carbapenem has higher OR in univariate analysis, it became insignificant while adding APACHE II score into the analysis system..

Table 2
Risk factors for mortality in ICU patients with IPA.

Variables	IPA (n = 90)	Survival (n = 46)	Death (n = 44)	p value
Medical center, No. (%)	64 (71.1)	34 (53.1)	30 (46.9)	0.724#
Female, no (%)	27 (30)	15 (55.6)	12 (44.4)	0.581
Age (mean ± SD)	65.3 ± 15.6	62.2 ± 16.7	68.6 ± 13.9	0.050
BMI (mean ± SD)	22.9 ± 8.1	23.3 ± 10.4	22.5 ± 4.8	0.658
Underlying diseases, No. (%)				
Diabetes mellitus	24 (26.7)	12 (50)	12 (50)	1.000#
Chronic obstructive pulmonary disease	5 (5.6)	3 (60)	2 (40)	1.000#
End-stage renal disease	7 (7.8)	3 (42.9)	4 (57.1)	0.711#
Liver cirrhosis	7 (7.8)	3 (42.9)	4 (57.1)	0.711#
Hematological malignance	6 (6.7)	4 (66.7)	2 (33.3)	0.677#
Solid organ transplant recipient	5 (5.6)	2 (40)	3 (60)	0.673#
Human immunodeficiency virus infection	1 (1.1)	1 (100)	0 (0)	1.000#
Autoimmune disease	2 (2.2)	1 (2.2)	1 (2.3)	1.000#
Solid cancer	22 (24.4)	11 (50)	11 (50)	0.905
Nasopharyngeal cancer	6 (6.7)	5 (83.3)	1 (16.7)	0.203#
Head & neck cancer	4 (4.4)	3 (75)	1 (25)	0.617#
Lung cancer	4 (4.4)	0 (0)	4 (100)	0.053#
Liver cancer	3 (3.3)	2 (66.7)	1 (33.3)	1.000#
Colorectal cancer	1 (1.1)	0 (0)	1 (100)	0.489#
Renal cancer	1 (1.1)	0 (0)	1 (100)	0.489#
Other cancers	4 (4.4)	2 (50)	2 (50)	1.000#
Charlson Comorbidity Index (mean ± SD)	4.9 ± 2.3	4.6 ± 2.3	5.2 ± 2.2	0.238
Steroid use (prednisolone or equivalent)				
> 5 mg/day, > 5 days, No. (%)	64 (71.1)	31 (48.4)	33 (51.6)	0.490
Daily dose (mg)	34.8 ± 21.6	26.6 ± 18.9	43.3 ± 21.1	< 0.001*
Total dose (mg)	583.4 ± 638.8	470.4 ± 652.2	701.5 ± 609.6	0.086
Duration (day)	15.8 ± 18.9	15.2 ± 22.4	16.5 ± 14.7	0.737
Severity status, No. (%)				
APACHE II score (mean ± SD)	20.6 ± 9.2	17.3 ± 8.5	24.2 ± 8.6	< 0.001*
SOFA score (mean ± SD)	7.5 ± 4.3	6.4 ± 4.1	8.7 ± 4.2	0.009*
Ventilator use, No. (%)	53 (58.9)	25 (47.2)	28 (52.8)	0.399
On ECMO, No. (%)	4 (4.4)	2 (50)	2 (50)	1.000#
Septic shock, No. (%)	83 (92.2)	40 (48.2)	43 (51.8)	1.111#
Chest X-ray finding, No. (%)				0.865#
Peribronchial infiltrations	12 (13.3)	6 (50)	6 (50)	
Bilateral lung patch infiltrates	16 (17.8)	7 (43.8)	9 (56.3)	
Multiple patches with necrotizing processes	22 (24.4)	12 (54.5)	10 (45.5)	
Diffuse ground-glass appearance	10 (11.1)	5 (50)	5 (50)	
Extensive consolidation on unilateral lung	18 (20)	11 (61.1)	7 (38.9)	
Extensive consolidation on bilateral lungs	3 (3.3)	2 (66.7)	1 (33.3)	
Diffuse air-space infiltration pattern	9 (10)	3 (33.3)	6 (66.7)	
ARDS, No. (%)	61 (67.8)	27 (44.3)	34 (55.7)	0.271
Mild	21 (23.3)	10 (47.6)	11 (52.4)	0.805
Moderate	24 (26.7)	11 (45.8)	13 (54.2)	0.636
Severe	16 (17.8)	6 (37.5)	10 (62.5)	0.277
PaO2/FiO2 ratio (mean ± SD)	259.8 ± 199.6	269.2 ± 167.3	250.4 ± 229.1	0.662
Laboratory data				
White blood cell count/μL (mean ± SD) × 1000	12.6 ± 8.5	12.6 ± 7.4	12.5 ± 9.5	0.946
Lymphopenia (< 1000/μL), No. (%)	61 (67.8)	30 (49.2)	31 (50.8)	0.656
C-reactive protein (mean ± SD)	156 ± 115.9	127.0 ± 121.4	185.7 ± 103.2	0.023*
Procalcitonin (mean ± SD)	20.8 ± 42.5	10.9 ± 26.0	28.9 ± 51.4	0.106
Platelet count/Ml (mean ± SD) × 1000	209.8 ± 124.9	225.2 ± 137.3	193.3 ± 109.2	0.231
Creatinine (mg/dL)	1.3 ± 0.9	1.2 ± 0.89	1.29 ± 0.91	0.726
Total-bilirubin (mg/dL)	1.9 ± 1.7	1.6 ± 1.7	2.1 ± 1.7	0.176
Community-acquired pneumonia, No. (%)	81 (90)	40 (49.4)	41 (50.6)	0.486#
Respiratory bacterial co-isolates, No. (%)	26 (28.9)	12 (46.2)	14 (53.8)	0.549
Blood stream infection, No. (%)	21 (23.3)	10 (47.6)	11 (52.4)	0.715
On carbapenem, No. (%)	25 (27.8)	8 (32)	17 (68)	0.024*
Antifungal therapy, No. (%)	50 (55.6)	20 (40)	30 (60)	0.018*
Voriconazole	44 (48.9)	18 (40.9)	26 (59.1)	0.091
Caspofungin	17 (18.9)	4 (23.5)	13 (76.5)	0.015*
Liposomal amphotericin B	6 (6.7)	3 (50)	3 (50)	1.000#
Anidulafungin	2 (2.2)	1 (50)	1 (50)	1.000#
Hospitalized duration				
ICU stay > 21 days, No. (%)	24 (26.7)	9 (37.5)	15 (62.5)	0.119
Hospitalization day (mean ± SD)	30.7 ± 24.2	34.9 ± 26.4	26.3 ± 21.0	0.088
Disease economic burden (NTD)				
Hospital cost (mean ± SD)	264672.9 ± 245734.6	209904.9 ± 176305.9	321930.4 ± 293071.6	0.032*
Drug fee (mean ± SD)	195834.5 ± 207426.8	144981.8 ± 148825.1	248998.6 ± 245389.2	0.018*

(*continued on next page*)

Table 2 (*continued*)

Laboratory fee (mean ± SD)	68838.8 ± 63585.7	64923.5 ± 48734.9	72932.0 ± 76480.4	0.553
Diagnosis criteria				
Day of galactomannan after hospital admission	10.6 ± 10.3	12.5 ± 11.7	8.9 ± 8.6	0.104
BAL galactomannan index (mean ± SD)	2.6 ± 2.6	2.5 ± 2.3	2.7 ± 3.1	0.848
Serum galactomannan index (mean ± SD)	1.5 ± 1.5	1.7 ± 1.7	1.2 ± 1.4	0.176

Abbreviations: ICU, intensive care unit; IPA, invasive pulmonary aspergillosis; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ECMO, extracorporeal membrane oxygenation; ARDS, acute respiratory distress syndrome; NTD, New Taiwan Dollar; BAL, bronchoalveolar lavage.
* $p < 0.05$
# Fisher's exact test

Difference between survival and death in the subgroup patients with and without antifungal therapy (Table 4)

Table is mainly to find difference of proportions in the risk factor for mortality between the subgroups. We found that subgroup patients with antifungal therapy who died received higher daily doses of steroids ($p = 0.024$) and had higher CRP levels ($p = 0.027$) than those who survived the event. Regarding the subgroup without antifungal therapy, the mortality patients were older aged ($p = 0.025$) and had higher daily doses of steroids ($p = 0.006$) as well as higher disease severity (both APACHE II and SOFA scores, $p < 0.001$)..

Stratified analysis: The risk factors predicting mortality of subgroup patients with and without antifungal therapy (Table 5)

Based on the above-mentioned potential risk factors for mortality, stratified logistic regression analysis of patients with IPA who received antifungal therapy found two independent risk factors for mortality: higher daily dose of steroids (OR = 1.046; 95% CI, 1.007–1.086; $p = 0.021$) and higher CRP level (OR = 1.006; 95% CI, 1.001–1.012; $p = 0.025$). In the subgroup analysis of patients with IPA without antifungal therapy, we found that mortality was significantly and independently associated with higher APACHE II score (OR = 1.232; 95% CI, 1.060–1.433; $p = 0.007$).

Patient-selection bias and subsequent outcomes: Difference between the patients with IPA with and without antifungal therapy (Tables 6 and 7)

The IPA cases in the study by retrospective definition do not necessarily mean that attending physicians would have treated the patients with anti-fungal agents during their primary care. Since patients with IPA with antifungal therapy had a significantly higher distribution in the mortality group than the survivors (60% vs. 40%, $p = 0.018$, Table 2), we believe that there would be a selection bias for antifungal therapy. To support this hypothesis, we compared the characteristics of patients who did not receive antifungal therapy with those of patients who received antifungal agents. We found that the treatment group had more steroid use, higher SOFA scores, and more severe ARDS than those without antifungal treatment (all $p < 0.05$, Table 6). In addition, the treatment group had significantly lower white blood cell and platelet counts than those without antifungal therapy (Table 6). In contrast, no significant difference was observed between the two groups in terms of age, sex, body mass index, distribution of comorbidity, APACHE II score, use of MV and ECMO, presence of septic shock, radiographic findings, and other initial inflammatory biomarkers such as CRP and procalcitonin (data not shown). Finally, patients receiving antifungal therapy had a longer ICU stay, longer length of hospital stay, and higher all-cause mortality than those without antifungal treatment (all $p < 0.05$), but no significant differences were observed on the GM test day and in its relevant data (Table 6). To find out the probable reasons for initiating antifungal therapy, further multivariable analysis by logistic regression identified three independent predictors: prolonged steroid use (OR = 6.694; CI = 2.152–20.827, $p = 0.001$), lower white blood cell count (OR = 0.392; CI = 0.877–0.989; $p = 0.021$), and higher SOFA score (OR = 1.138, CI =1.001–1.294; $p = 0.048$) in the final forward approach model (Table 7).

Discussion

This multicenter study investigated the clinical manifestations of 90 patients with IPA without influenza in ICUs. Overall, this study provided a comprehensive view of IPA and helped us better understand the clinical characteristics of IPA in the ICU. We had several significant findings. First, we found that the most common traditional immunocompromised disorder in this study was observed in 70% of patients who had received steroids before acquiring IPA. This finding indicates that steroids could be a risk factor for IPA among critically ill patients in the ICU. Furthermore, an unstable clinical status, including septic shock and ARDS, was observed in more than 80% and 60% of patients, respectively, highlighting the heavy therapeutic burden of these patients. Nonetheless, only 58.9% (53/90) of them required mechanical ventilation support, probably due to the reasons (1) 73.8% of ARDS were mild-to-moderate, and (2) 55.6% (50/90) of them did not have extensive lung involvement. About 90% of patients had community-acquired pneumonia. It might also remind clinicians to be alert for the possible presence or development of IPA among patients in the ICU with pneumonia and these unstable clinical conditions, particularly in a host with traditional or modified immunocompromised conditions. However, most of the imaging

Table 3
Logistic regression analysis of potential risk factors for in-hospital mortality in patients with non-influenza IPA.

Variables	Univariate			Multivariable (full model)			Multivariable (forward approach)		
	Odds Ratio	95% CI	*p* value	Odds Ratio	95% CI	*p* value	Odds Ratio	95% CI	*p* value
Age	1.028	0.999–1.058	0.054	1.058	1.016–1.102	0.007	1.052	1.011–1.094	0.013
Steroid daily dose	1.047	1.019–1.074	0.001	1.053	1.015–1.092	0.006	1.057	1.021–1.095	0.002
APACHE II score	1.099	1.040–1.160	0.001	1.076	0.989–1.171	0.088	1.094	1.020–1.174	0.012
SOFA score	1.151	1.031–1.285	0.012	1.076	0.885–1.308	0.462			
C-reactive protein	1.005	1.001–1.009	0.027	1.007	1.002–1.013	0.012	1.007	1.002–1.012	0.008
On carbapenem	2.991	1.129–7.924	0.028	2.841	0.670–12.048	0.157			
Antifungal therapy	2.786	1.177–6.593	0.020	2.060	0.527–8.046	0.299			
On caspofungin	4.403	1.309–14.810	0.017	0.996	0.176–5.637	0.997			

Note. IPA, invasive pulmonary aspergillosis; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

Table 4
Risk factors for mortality in ICU patients with IPA stratified by subgroups of receiving antifungal therapy or no antifungal therapy.

Variables	Antifungal therapy (n = 50)	Survival (n = 20)	Death (n = 30)	p value
Age (mean ± SD)	63.6 ± 16.2	60.2 ± 17.9	65.8 ± 14.7	0.227
Steroid Daily dose (mg)	38.43 ± 22.4	29.8 ± 18.7	44.2 ± 23	0.024
APACHE II score (mean ± SD)	22.0 ± 9.3	20.7 ± 9.9	22.9 ± 8.9	0.415
SOFA score (mean ± SD)	8.4 ± ± 4.3	8.5 ± 4.1	8.4 ± 4.5	0.990
C-reactive protein (mean ± SD)	164.1 ± 123.9	117.7 ± 138.9	197.3 ± 101.9	0.027
On carbapenem (n%)	16 (100%)	4 (25%)	12 (75%)	0.137
On caspofungin (n%)	17 (100%)	4 (23.5%)	13 (76.5%)	0.088
Variables	No antifungal therapy (n = 40)	Survival (n = 26)	Death (n = 14)	p value
Age (mean ± SD)	67.6 ± 14.9	63.8 ± 15.8	74.6 ± 10.0	0.025
Steroid daily dose (mg)	30.2 ± 19.9	24.1 ± 19.0	41.5 ± 16.8	0.006
APACHE II score (mean ± SD)	19 ± 8.9	14.7 ± 6.1	27 ± 7.5	< 0.001
SOFA score (mean ± SD)	6.4 ± 4.0	4,8 ± 3.3	9.4 ± 3.5	< 0.001
C-reactive protein	143.4 ± 103.0	136.4 ± 103.9	156.2 ± 105.1	0.616
On carbapenem (n%)	9 (100%)	4 (44.4%)	5 (55.6%)	0.142

Table 5
Logistic regression analysis of potential risk factors for in-hospital mortality in patients with and without antifungal therapy.

Variables	Univariate			Multivariable (full model)			Multivariable (forward approach)		
	Odds Ratio	95% CI	p value	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
IPA patients with antifungal therapy									
Age	1.023	0.986–1.061	0.225	1.032	0.987–1.708	0.163			
Steroid daily dose	1.037	1.003–1.072	0.033	1.045	1.002–1.089	0.039	1.046	1.007–1.086	0.021
APACHE II score	1.027	1.964–1.094	0.408	1.050	0.961–1.146	0.278			
SOFA score	0.999	1.875–1.140	0.989	0.984	0.797–1.214	0.878			
C-reactive protein	1.006	1.000–1.011	0.033	1.007	1.001–1.013	0.017	1.006	1.001–1.012	0.025
PA patients without antifungal therapy									
Age	1.062	1.004–1.124	0.035	1.158	1.009–1.331	0.038			
Steroid daily dose	1.054	1.010–1.099	0.016	1.104	0.994–1.227	0.064			
APACHE II score	1.276	1.105–1.473	0.001	1.377	1.059–1.789	0.017	1.232	1.060–1.433	0.007
SOFA score	1.502	1.145–1.969	0.003	1.286	0.800–2.066	0.299	1.395	0.971–2.005	0.072

Note. IPA, invasive pulmonary aspergillosis; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

features of chest X-rays in the ICU patients with IPA were not significantly different from those of bacterial pneumonia, suggesting difficulty in the differential diagnosis between them and that physicians should not rely on the typical cavitary lesions of IPA to initiate a diagnostic approach, similar to our previous report of IPA in severe influenza patients [13]. In addition, physicians should not rely on the high levels of positive serum or BAL GM index to initiate antifungal therapy, as they did not correlate well with mortality in the current study.

Second, almost half of the patients (44.4%) did not receive antifungal treatment in this study. Although antifungal therapy did not play an independent role in mortality in multivariable analysis, we need to retrospectively discuss why ICU physicians decided not to treat patients with IPA. In these ICUs, the prescription of antifungal

Table 6
Clinical differences in IPA patients with and without antifungal therapy.

Variables	Group (n = 90)	Antifungal therapy (n = 50)	No antifungal therapy (n = 40)	p value
Steroid use (prednisolone or equivalent)				
> 5 mg/day, > 5 days, No. (%)	64 (71.1)	44 (68.8)	20 (31.3)	< 0.001
Daily dose (mg)	34.8 ± 21.6	38.4 ± 22.4	30.2 ± 19.9	0.072
Total dose (mg)	583.4 ± 638.8	772.6 ± 723.5	346.8 ± 412.8	0.001
Duration (day)	15.8 ± 18.9	20.7 ± 22.4	9.8 ± 10.8	0.003
Severity status				
APACHE II score (mean ± SD)	20.6 ± 9.2	22.0 ± 9.3	19.0 ± 8.9	0.124
SOFA score (mean ± SD)	7.5 ± 4.3	8.4 ± 4.3	6.4 ± 4.0	0.022
Severe ARDS, No. (%)	16 (17.8)	13 (81.3)	3 (18.8)	0.027
White blood cell count/μL (mean ± SD) × 1000	12.6 ± 8.5	10.5 ± 7.8	15.1 ± 8.6	0.010
White blood cell count ≦ 4000/μL, No. (%)	17 (18.9)	14 (82.4)	3 (17.6)	0.016
White blood cell count ≧ 10000/μL, No. (%)	58 (64.4)	27 (46.6)	31 (53.4)	0.027
Platelet count/μL (mean ± SD) × 1000	209.8 ± 124.9	175.1 ± 112.4	254.4 ± 127.2	0.003
Clinical outcome				
ICU stay > 21 days, No. (%)	24 (26.7)	18 (75)	6 (25)	0.032
Hospitalization day (mean ± SD)	30.7 ± 24.2	37.3 ± 28.0	22.4 ± 14.8	0.003
Mortality, No. (%)	44 (48.9%)	30 (68.2)	14 (31.8)	0.018
Diagnosis criteria				
Day of GM testing after hospital admission	10.6 ± 10.3	12.2 ± 11.2	8.7 ± 8.9	0.103
BAL GM Index	2.6 ± 2.6	2.9 ± 2.6	2.3 ± 2.7	0.552
Serum GM Index	1.5 ± 1.5	1.6 ± 1.6	1.3 ± 1.4	0.299

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage.

Table 7
Risk factors for mortality in IPA patients (n = 90) with and without antifungal therapy based on selection bias.

Variables	Antifungal therapy (n = 50)	No antifungal therapy (n = 40)	p value
Physicians' selection bias for therapy	Prolonged steroid use	Shorter steroid use	0.001[a]
	Higher SOFA score	Lower SOFA score	0.048[a]
	Lower white blood cell count	Higher white blood cell count	0.021[a]
Clinical outcomes			
ICU stay > 21 days	36% (18/50)	15% (6/40)	0.032[b]
Hospitalization day (mean)	37.3	22.4	0.003[b]
In-hospital mortality	60% (30/50)	35% (14/40)	0.018[b]
Independent risk factors for mortality	Steroid daily dose (p = 0.021)[c]	APACHE II score (p = 0.007)[c]	
	C-reactive protein (p = 0.025)[c]		

Abbreviations: SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation
[a] The p-values were derived from multivariable analysis by logistic regression final models.
[b] The p-values were derived from Chi-square test in Table 6.
[c] The p-values were derived from multivariable analysis by logistic regression final models in Table 5.

agents was based on the discretion of the in-charge physicians, who might try to avoid overtreating the suspicious cases empirically. Possible reasons could be explained by the following two factors. The first reason is that antifungal agents are expensive in Taiwan, and most uses of antifungal treatment are targeted rather than empirical therapy. However, the GM experiments were performed only twice a week in our institutes, and thus the data might not be available in time and the diagnosis of IPA might be confirmed after the patient's death, which could partly explain why these patients did not receive antifungal treatment [22]. In fact, the mortality of the untreated group was not low (14/40, 35%), which was similar to that of patients with IPA in the nationwide inpatient population (30.2%), according to an 11-year follow-up study in Taiwan [23]; and was rather higher than 28-day mortality rates (15–20%) in critically ill patients with respiratory virus-related pneumonia from a recent report in Taiwan [24]. A large proportion of the cohort cases did not receive antifungal treatment implying broad application of GM testing but rather conservative decision-making by physicians in antifungal therapy. However, the no-treatment group does not really mean no need to treat for IPA at all, reflecting the difficult situation of managing IPA in real-world clinical practice. Our study revealed that patient-selection bias for antifungal therapy included prolonged steroid use, lower white blood cell count, and higher SOFA score in the final model of multivariable analysis. Based on the selection bias, the associated risk factors for mortality were higher daily doses of steroids and higher CRP levels in the treatment group as well as higher APACHE II scores in the untreated group. Physicians should be cautious when conducting GM experiments for suspected IPA in patients, particularly those with these risk factors for mortality, and empirical or early antifungal therapy should be considered. The second reason concerns the accuracy of IPA diagnosis. In this study, some physicians did not prescribe antifungal agents for patients with a high white blood cell count, lower disease severity, or less steroid use, which seemed less likely *Aspergillus* infections. In line with our previous study [3], 56.5% (26/46) of the patients with IPA did not receive antifungal agents but survived. Therefore, the above reasons for selection bias could also help explain why patients receiving antifungal treatment had worse outcomes, such as a longer ICU stay, longer length of hospital stay, and higher mortality than those without antifungal treatment in the Chi-square test.

However, it might still be frustrating that the antifungal treatment group had a significantly higher mortality of 60% (30/50) than those without antifungal therapy (35%). Therefore, we performed a subgroup analysis according to the antifungal agents. The antifungal treatment subgroup of patients initially receiving caspofungin showed significantly higher mortality (76.5% death vs. 23.5% survival, p = 0.015). Although 13/17 (76.5%) patients were subsequently revised to voriconazole, their mortality remained high (73.9%, 10/13). Therefore, our data did not support the initial caspofungin therapy for IPA in critically ill patients. Since patients in the treated group had prolonged steroid use and higher SOFA scores, under such circumstances, the risk factors for mortality in this group were associated with the higher steroid daily dose and higher CRP level, but not with the severity scores. Similarly, the use of voriconazole was not significantly associated with a higher survival rate (p = 0.323) in a nationwide Taiwanese IPA study [23]. Overall, antifungal therapy could not successfully improve outcomes, indicating the unmet need for more effective antifungal regimens than our available agents for IPA in critically ill patients.

Third, co-bacterial infections were observed in 28.9% of patients, and bloodstream infections occurred in 23.3% during the course. These co-infections might potentially confound the mortality analysis, which was demonstrated in a previous study that other infectious diseases could be one of the predictive factors for mortality in patients with IPA (p = 0.0008) [23]. In the present study, these co-infections did not play a significant role in contributing to mortality based on Chi-square distribution and univariate analysis. A possible cause could be that the patients received appropriate antimicrobial agents. For example, carbapenems were used in 27.8% of the patients with IPA and thus were not an independent factor contributing to in-hospital mortality in multivariable analysis, even though this factor was associated with mortality using Chi-square distribution and univariate analysis.

Fourth, regarding general risk factors for mortality, in line with previous studies [1,3,8], the mortality of patients with IPA in this study remained substantially high (48.9%) and was independently associated with older age, higher daily steroid dose, higher APACHE II score, and higher CRP level by multivariable analysis. We previously reported that the risk factors for mortality in patients with concomitant severe influenza and IPA included patients' Charlson comorbidity index, APACHE II score, and severe ARDS [3]. The current study reported that non-influenza patients with IPA had some different risk factors for mortality in comparison to influenza patients. We particularly emphasize the factor of daily steroid dose, which would be easily neglected as the risk matter when corticosteroid is used for ICU patients with septic shock. Early diagnosis is also mandatory to receive antifungal therapy in time, especially for those patients with a high APACHE II score, which independently predicted mortality in those without antifungal therapy.

Lastly, our data revealed that about 90% of patients had community-acquired pneumonia and higher daily steroid dose significantly contributed to in-hospital mortality, especially in the subgroup being selected to receive antifungal therapy. Recent studies have suggested corticosteroid benefit of a lower risk of death in the treatment of severe community-acquired pneumonia [25,26]. However, we recommend the prudent use of corticosteroids for severe community-acquired pneumonia in ICU patients probably with IPA.

This study had several limitations. First, the current study did not compare the group of patients with concurrent IPA and influenza

infection. In our previous study [3], the influenza patients coinfected with IPA had a mortality of 50% (20/40). However, in the current study, IPA alone did contribute to substantially high mortality of 48.9% (44/90) in the absence of influenza coinfection. Second, other potential factors associated with mortality might not be included in the current study. Exploring a larger sample size in future studies may develop a more clinically meaningful models that capture a broader range of contributing factors. Third, the *Asp*ICU algorithm developed by Blot et al. was the original criterion requiring a positive culture for *Aspergillus* as an entry criterion for IPA in ICU patients [27]. However, this algorithm was not applicable in our study, as very few cultures (4.4% [4/90]) were positive in the study cases, which was similar to a positive culture rate of 9.68% (3/31) in a study in China (p = 0.282) [19]. One of the potential impacts of the fact was that all the patients included in this study have probable (but not confirmed) IPA. Fourth, approximately 90% of patients presented with community-acquired pneumonia, and GM testing was performed at a mean of 10.6 days after hospital admission. It is difficult to discern the true onset of IPA; nonetheless, earlier diagnosis with prompt treatment may improve outcomes [28]. Fifth, the determination of GM in serum can be erratic in non-neutropenic patients; however, serum GM was positive in 72 (80%) of the 90 cohort patients in this study, indicating the applicability of serum GM in non-neutropenic patients. In addition, there was no specific protocol for the diagnosis of IPA in our institutes, and thus only a third of the included cohort patients underwent bronchoalveolar lavage during the study period. Therefore, underdiagnosis and delay diagnosis of aspergillosis could be possible. Lastly, since the coronavirus disease 2019 (COVID-19) pandemic has changed the epidemiology of IPA [29,30], the impact of COVID-19 on the outcome of IPA will be studied in ongoing research separately.

In conclusion, the mortality of critically ill patients with IPA remained high and was associated with older age, higher daily steroid dose, higher disease severity, and higher CRP level based on overall multivariable analysis. Nearly half of the patients in this study did not receive antifungal agents, probably based on an assumption of less likely IPA, such as those with a higher white blood cell count, lower SOFA score, and short-term steroid use. With the potential selection bias for antifungal therapy, the risk factors for mortality would be different while stratified by subgroup analysis. The decision-making process regarding antifungal treatment is complex; however, their use should be considered when treating critically ill patients at high risk of mortality, such as those with high disease severity or receiving systemic steroids. Finally, coinfection was not uncommon in patients with IPA; thus, physicians should be alert about the occurrence of coinfection in critically ill patients with IPA.

Ethics approval

We declare compliance with ethical standards as process was approved by the Institutional Review Board of the Chi Mei Medical Center (IRB No. 10801–002).

Consent for publication

Not applicable.

Potential conflicts of interest

The authors have no potential conflicts.

Funding

This work was funded by Merck & Co., Inc., USA (Project No. MISP #57761).

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

We have no conflict of interest to declare.

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