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CLINICAL FEATURES, OUTCOMES AND COMPARATIVE EVALUATION OF DIAGNOSTIC CRITERIA OF INVASIVE ASPERGILLOSIS AT A TERTIARY CARE CENTRE: A RETROSPECTIVE OBSERVATIONAL STUDY

Surkunda T S.[1], Stanley W.[1], Elenjickal V.[2]*, Ballal A.[1], Nagaraju S.[1], Boppe S.[1], Kamath N.[1], Shastry B.[1]

[1]. Department of General Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

[2]. Department of Respiratory Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

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Abstract

Introduction: *To compare EORTC/MSGERC and BM-AspICU diagnostic criteria for invasive aspergillosis and analyse clinical, mycological, and radiological features affecting patient outcomes.*

Materials and Methods*: We conducted a retrospective study on 56 invasive aspergillosis patients who met inclusion criteria (age >18 years and confirmed diagnosis via histopathology, cultures, or galactomannan). Patients were categorized using EORTC/MSGERC and BM-AspICU criteria. Clinical, microbiological, radiological data, and outcomes were analysed.*

Results*: of 56 patients, 47 had invasive pulmonary aspergillosis, 7 had invasive rhinosinusitis, 1 had disseminated, and 1 had cerebral aspergillosis. Mean age was 51.5 years, with 75% (42) males. Aspergillus fumigatus was common species (47.3%) isolated. Computed tomography scans of invasive pulmonary aspergillosis often showed nonspecific infiltrates (31.9%). Voriconazole was most used antifungal (80.4%). Mortality was 23.2% (n=13) in total and in intensive care unit patients with invasive pulmonary aspergillosis was 46.1% (n=12). 75% (9/12) of deceased patients initially classified as pulmonary colonizers by EORTC/MSGERC were reclassified as probable (n=3) or possible (n=6) invasive aspergillosis cases by BM-AspICU, difference was statistically significant (p=0.019). Intensive care unit admission was 55.3% (median stay: 8 days), higher in viral pneumonia (p = 0.003). Univariate analysis of invasive pulmonary aspergillosis patients showed significant mortality correlations with shock (p=0.001), acute kidney injury (p=0.003), invasive mechanical ventilation (p=0.001) and intensive care unit stay (p=0.026). Multivariate analysis identified shock as an independent predictor of mortality.*

Conclusion*: In our study, BM-AspICU criteria demonstrated a stronger correlation with mortality compared to EORTC/MSGERC criteria. Morbidity and mortality were associated with viral pneumonia, shock, acute kidney injury, invasive mechanical ventilation and intensive care unit stay.*

Keywords: *Invasive aspergillosis, BM-AspICU criteria, invasive pulmonary aspergillosis.*

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Address for Correspondence:

Vrinda Mariya Elenjickal, MD, Assistant Professor,
Department of Respiratory Medicine, Kasturba Medical
College, Manipal Academy of Higher Education, Tiger Circle
Road, Madhav Nagar, Manipal, Karnataka, 576104, India
Tel.: (+91) 9986822148
E-mail: vrinda.me@manipal.edu

Introduction

Aspergillus species are omnipresent in the environment, and humans inhale hundreds to thousands of spores daily. Both innate immunity and adaptive immunity interact synergistically to eliminate these spores and prevent the invasion of potentially pathogenic hyphae into tissues [*Lass-Flörl C et al., 2013*]. Immune dysfunction or immunosuppression of any form renders individuals susceptible to various diseases caused by Aspergillus species [*Chotirmall SH et al., 2013*]. Ultimately, the interaction between the host, the fungus, and the microenvironment determines not only the type of disease but also the outcome in each patient [*Obar JJ et al., 2016*].

The diagnosis of invasive aspergillosis is complicated by several factors, including difficulties in obtaining biopsies due to hemodynamic instability, coagulation abnormalities, or the need for high levels of ventilatory support; challenges in differentiating colonization from infection in respiratory samples; limited sensitivity of cultures from blood and sterile sites; and frequently non-specific nature of clinical and radiological findings [*Azim A, Ahmed A, 2024*]. Earlier diagnostic criteria focused primarily on patients with haematological malignancies or solid organ transplant recipients and are recommended for research and epidemiological purposes [*Ascioglu S et al.,2002, De Pauw B et al., 2008*]. With the increasing incidence of invasive aspergillosis in critically ill intensive care unit (ICU) patients, newer criteria [*Blot S et al.,2012*; *Schauwvlieghe A et al., 2018*; *Hamam J et al., 2021*] and revisions of existing criteria [*Donnelly J et al., 2020*; *Bassetti M et al., 2021*] have been proposed for this patient population.

There are few studies that have included invasive aspergillosis in medical ward settings; thus, in our study, we aimed to study the clinical, radiological, and mycological profiles of patients diagnosed with invasive aspergillosis in both intensive care unit and medical ward settings while assessing the factors associated with morbidity and mortality [*Corcione S et al., 2021*]. Additionally, we compared the recent European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) host factor criteria [*Donnelly J et al., 2020*] with the novel BM-AspICU criteria [*Hamam J et al., 2021*] in patients diagnosed with invasive pulmonary aspergillosis.

Materials and Methods

Study design: This retrospective observational study was conducted at a teaching hospital in southern India with approval from the Institutional Ethics Committee (IEC Ref. No. 855/2021). Informed consent was waived as per IEC guidelines. Clinical Trials Registry (India) registration was not applicable due to the retrospective design.

Study population: Medical records of 310 patients were retrieved using ICD codes B44.0, B44.1, B44.8, and B44.9 from January 2016 to December 2022. Among these, 99 patients were diagnosed with invasive aspergillosis. We applied entry criteria of age >18 years and positive histopathology, culture, bronchoalveolar lavage galactomannan, or serum galactomannan, enrolling 56 patients after excluding those under 18 years and those diagnosed solely on clinical suspicion and radiological findings. These 56 patients were categorized based on the EORTC/MSGERC and BM-AspICU criteria. Clinical presentations, microbiological and radiological features, and patient outcomes were collected and analysed.

Statistical analysis: Data were summarized using appropriate descriptive statistics, including range, mean ± standard deviation (SD), median with interquartile range (IQR), frequency (number of cases), and percentage. The Kolmogorov–Smirnov test was utilized to evaluate the normality of data distribution. For group comparisons involving quantitative variables, the Mann–Whitney U test was employed for nonparametric data. Categorical variables were compared using the chi-square (χ^2) test, with Fisher's exact test applied when the expected frequency was below 5. Variables with a P-value less than 0.05 in univariate analysis were entered into a multivariate binary logistic regression model. Statistical significance was defined as a P-value <0.05. All analyses were conducted using SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows.

Results

Organ affected and diagnostic categorization: Among the 56 patients, 47 were invasive pulmonary aspergillosis (IPA)**,** including one case of invasive tracheobronchitis**,** seven had invasive rhinosinusitis, one had disseminated (sinopulmonary) aspergillosis, and one had isolated invasive cerebral

aspergillosis. According to the EORTC/MSGERC criteria, nine cases were classified as proven invasive aspergillosis (five with rhinosinusitis, two with pulmonary aspergillosis, one with disseminated aspergillosis, and one with cerebral aspergillosis), while two cases were probable (pulmonary), and one case was possible (pulmonary). The remaining 44 patients were classified as colonizers (42 pulmonary and two rhinosinusitis patients).

Although the BM-AspICU criteria were originally developed to identify critically ill invasive pulmonary aspergillosis patients admitted to the intensive care unit (ICU), we extended the application of these criteria to patients admitted to medical wards in our study. This adaptation allowed us to categorize cases systematically and compare both the BM-AspICU and EORTC/MSG criteria in a broader patient population. According to the BM-AspICU criteria, among the 47 patients with invasive pulmonary aspergillosis, two were classified as proven, 23 as probable, 21 as possible, and one as colonization. Among the 42 patients categorized as pulmonary colonizers under the EORTC/MSGERC, 20 were classified as probable, 21 as possible, and one as colonization per the BM-AspICU criteria.

Study population and clinical characteristics: Among fifty-six patients diagnosed with invasive aspergillosis, 25 (44.6%) were admitted to the ward and 31 (55.4%) to the intensive care unit. Various characteristics of the patients who were admitted in the ward and intensive care unit have been summarized in Table 1. The mean age of the study population was 51.5 ± 15.7 years, with males having a mean age of 50 ± 16 years and females having a mean age of 54 ± 13 years. Among the patients, 42 (75%) were males, and 14 (75%) were females. The most common comorbid condition was diabetes, which was present in 20 (36.7%) patients. Additionally, 14 patients (25%) had viral pneumonia, including 11 with COVID-19-associated pulmonary aspergillosis and 3 with influenza-associated pulmonary aspergillosis. Other comorbidities included chronic kidney disease in 7 patients (12.5%), one of whom had received a renal transplant; Chronic obstructive pulmonary disease in 5 patients (8.9%); chronic liver disease in 3 patients (5.4%); retroviral disease in 6 patients (10.7%); neutropenia in 6 patients (10.7%); haematological malignancy in 4 patients (7.1%), all of whom were receiving chemotherapy; and solid malignancy in 2 patients (3.6%), both of whom were receiving chemothera-

TABLE 1.

Comparison of various characteristics of patients (N=47) with Invasive pulmonary aspergillosis admitted to the intensive care unit and medical ward

Characteristics	Intensive care unit ***(nb=28)***	Medical ward. (19)	***p value***
Dermographic features			
Age (mean±SD)	57.0 ±14.8	51.1 ±12.4	***0.16***
Male gender	21(75)	13 (68.4)	***0.621***
Symptoms			
Persistent fever, n (%)	13(46.4%)	12(63.2%)	0.259
Dyspnoea at admission, n (%)	18(64.3%)	11(57.95%)	0.658
Haemoptysis, n (%)	3(10.7%)	-	0.262
Chest pain, n (%)	1(3.6%)	4(21.1%)	0.142
Comorbidities			
Present, n (%)	17 (60.7%)	11(57.9%)	0.847
Absent, n (%)	9(32.1%)	5(26.3%)	0.771
Diabetes, n (%)	12(42.9%)	6(31.6%)	0.435
Retroviral disease, n (%)	2(7.1%)	4(21.1%)	0.204
Hematological malignancy	1(3.6%)	2(10.5%)	0.557
Solid organ malignancy, n (%)	1(3.6%)	1(5.3%)	0.778
Chronic kidney disease, n (%)	6(21.45)	1(5.3%)	0.127
Chronic obstructive pulmonary disease, n (%)	1(3.6%)	4(21.1%)	0.412
Chronic liver disease; , n (%)	1(3.6%)	2(10.5%)	0.338
Viral pneumonia, n (%)	13(46.4%)	1 (5.3%)	**0.003***
EORTC host factors, n (%)	4 (14.3%)	3(15.8%)	0.887
Laboratory Features			
Culture positive, n (%)	7(25%)	7(36.8%)	0.381
Histopathology-proven cases, n (%)	1(3.6%)	1(5.3%)	0.447
Bronchoalveolar lavage; performed, n (%)	11 (39.3%)	17 (89.5%)	**0.001***
Bronchoalveolar lavage galactomannan antigen- positive, n (%)	9(32.1%)	14(73.7%)	**0.003***
Serum galactomannan antigen positive, n (%)	26 (92.9%)	12(63.2%)	**0.026***
Neutropenia, n (%)	3(10.7%)	2(10.5%)	0.984
Computed tomography performed as per EORTC criterias			
Typical findings, n (%)	12(42.9%)	4(21.1%)	0.299
Atypical findings, n (%)	11(39.3%)	10(52.6%)	0.299

NOTES: *(*) -p < 0.05 was considered statistically significant*

py. Eight patients (12.8%) had EORTC host factors (Hematologic malignancy or stem cell transplantation recipients, solid organ transplantation with immunosuppression, neutropenia (absolute neutrophil count <500 *cells/μL* for >10 days), prolonged steroid use (≥0.3 *mg/kg* per day prednisone for >3 weeks in the past 60 days), T-cell immunosuppression, and inherited immunodeficiencies, Acute graft-versus-host disease grade III or IV). Significant steroid usage (≥0.3 *mg/kg* corticosteroids for ≥3 weeks within the past 60 days) was observed in 7 patients (12.5%).

The clinical manifestations included persistent fever in 26 patients (46.4%), recurrent fever after initial subsidence in 1 patient (1.8%), haemoptysis in 3 patients (5.4%), chest pain in 5 patients (8.9%), and new onset or worsening respiratory failure after admission in 20 patients (35.7%).

Mycology and histopathology findings: Among the 56 cases, cultures were sent for 52 patients, 19 (33.9%) of whom were culture positive. Among the culture-positive cases, bronchoalveolar lavage yielded positive results in seven cases, endotracheal aspirate in four cases, sputum and tissue cultures in three cases each, and pus culture in two cases. *Aspergillus fumigatus* was isolated from 9 patients (47.3%), *Aspergillus flavus* was isolated from 6 patients (31.5%), *Aspergillus terreus* was isolated from 2 patients (10.5%), and other species were isolated from 2 patients (10.5%). Biopsy was performed in 12 patients, and histopathological confirmation of the diagnosis was obtained in 9 patients. bronchoalveolar lavage was performed in 28 cases, and bronchoalveolar lavage galactomannan testing was conducted in 23 cases, all of which yielded positive results. Serum galactomannan testing was carried out in 42 patients, with 2 patients yielding negative results. Among patients with IPA, bronchoscopy was more frequently performed in 17 (89.5) patients admitted to the ward than in 11 (39.3%) patients in the intensive care unit. Patients in the intensive care unit had significantly more serum galactomannan positivity (92.9% vs 63.2%) compared to medical ward.

Imaging findings: Among the 47 patients with IPA, 37 patients underwent chest computed tomography (CT). Sixteen of these patients had typical features of invasive aspergillosis according to the EORTC/MSGERC 10 criteria (dense, well-circumscribed lesions with or without halo sign, air crescent sign, cavity, wedge shape, and segmental or lobar consolidation). The remaining 21 patients had atypical features of invasive aspergillosis (non-cavitary nodules; peribronchial consolidations; diffuse ground-glass opacities without nodules; tree-in-bud appearance; pleural effusion; bronchiectasis).

The most common CT findings in our study were nonspecific infiltrates in 15 patients (31.9%), followed by the halo sign with or without consolidation in 6 patients (12.8%), ground-glass opacities in 4 patients (8.5%), cavitation with or without consolidation in 4 patients (8.5%), wedge consolidation in 3 patients (6.4%), nodules in 2 patients (4.3%), bronchiectatic changes in 2 patients (4.3%), and the air crescent sign in 1 patient (2.1%). Among the seven patients with invasive rhinosinusitis, CT of the paranasal sinuses was performed in all of them (six in the preoperative period and one in the postoperative period). In all six of these patients, bony erosions were observed on CT.

Treatment and outcomes: Among the 56 patients, two were discharged against medical advice, three were lost to follow-up, and 38 were alive one-month post-discharge. A total of 13 patients (23.2%) died, including 12 with IPA and one patient with acute myeloid leukemia and disseminated aspergillosis. Mortality in intensive care unit patients with IPA was 46.1% (n=12). Among those who died, three had diabetes, three had chronic kidney disease, two had haematological malignancies, one had retroviral disease, one had solid malignancy, and one had significant steroid use. Intensive care unit admission was required for 31 patients (55.3%), with a median intensive care unit stay of 8 days (IQR 4–16). Intensive care unit admission rates were significantly higher in patients with viral pneumonia (n/n; 13/14) ($p = 0.003$). Additionally, 16 patients (28.6%) required invasive mechanical ventilation (IMV), 11 (19.6%) developed new-onset or worsening acute kidney injury, and 14 (25%) required vasopressor support. No deaths were recorded in patients with chronic obstructive pulmonary or chronic liver diseases. Antifungal treatment included voriconazole in 45 patients (80.4%), itraconazole in 10 (17.9%), and amphotericin, followed by voriconazole in one patient. No deaths occurred among those treated with

itraconazole (0/9), while 13 deaths were reported in patients who received voriconazole (13/41).

After a complete case analysis of patients with IPA admitted to intensive care unit, mortality was observed in 80% (12/15) of those requiring invasive mechanical ventilation, 85.7% (12/14) requiring vasopressor support, 63.6% (7/11) with acute kidney injury, 50% (6/12) with viral pneumonia, and 64.7% (11/17) who experienced new-onset or worsening respiratory failure after admission. Comparison of characteristics between patients who survived and those who died among patients with IPA have been summarized in Table 2.

Discussion

The incidence of invasive aspergillosis in medical ICUs is generally reported to be low, but it is associated with higher mortality rates than patients with other infections or no infections. In our study, the overall mortality rate was 23.2%, and in ICU patients with invasive pulmonary aspergillosis, it was 46.1%, which is comparable to other studies (30–46%) [*Baddley J et al.,2013*; *Sun K et al.,2017*]. Diagnosing invasive aspergillosis remains difficult, especially in critically ill patients, due to inconsistencies in diagnostic criteria across populations and the challenges associated with obtaining tissue samples and performing diagnostic tests. These challenges frequently delay treatment initiation, resulting in more extended hospital stays, higher medical costs, and increased mortality. Previous studies have demonstrated significant differences in the sensitivity and specificity of criteria as well as correlation with mortality [*Dabas Y et al.,2018; Schroeder M etal.,2022*; *Liu R et al.,2023*]. In our study, we observed a significantly greater number of cases of probable IPA diagnosed via the BM-AspICU criteria than via the EORTC/MSGERC criteria (23 vs. 2, p = 0.008). This result is consistent with a study conducted in patients in the intensive care unit [*Ebner J etal.,2022*]. Furthermore, in our study, 75% (9/12) of the patients with invasive pulmonary aspergillosis who died were classified as pulmonary colonizers according to the EORTC/MSGERC criteria. In contrast, these same patients were categorized as either probable (n = 3) or possible (n = 6) cases of invasive aspergillosis using the BM-AspICU criteria, a statistically significant finding (p = 0.019). This suggests that, in this cohort, the BM-AspICU criteria demonstrated a stronger correlation with mortality compared to the EORTC/MSGERC criteria.

In our study, medical ward patients with IPA were classified using the BM-AspICU criterion, which was initially developed for ICU settings. Apart from serum galactomannan positivity, viral pneumonia, and the number of bronchoalveolar lavage tests performed, no significant differences were observed between groups. While BM-AspICU criteria may not fully capture the clinical spectrum of IPA outside the ICU, it offers a valuable foundation for further adaptation. As most medical ward patients lack classic EORTC host factors, diagnosing invasive aspergillosis remains challenging. Our findings suggest that a modified application of this criterion could serve as a practical alternative in this population.

Invasive tracheobronchitis is linked to a poor prognosis and high mortality (90%), as evidenced by a study conducted by Nyga R with co-authors (*2020*) [*Nyga R et al, 2020*]. In our study, one patient who was diagnosed with invasive tracheobronchitis died. Cerebral invasive aspergillosis is typically a secondary complication of invasive sinus aspergillosis in immunocompetent individuals, often resulting in mixed outcomes [*Taha MS et al.,2021*]. Isolated cerebral aspergillosis is a rare occurrence, and one young diabetic patient in our study had a favourable outcome, a similar finding, which was also reported by Bokhari R with co-authors [*Bokhari R et al.,* 2014].

Among the seven patients diagnosed with invasive fungal sinusitis, all patients underwent biopsy and histopathological analysis, which confirmed five patients. The remaining two patients had positive tissue cultures, with bony erosion observed on CT of the paranasal sinuses. Two patients developed complications, including orbital extension in a clinically healthy individual and intracranial extension in a patient with diabetes mellitus, both of whom underwent surgical intervention with favourable outcomes. Early surgical intervention has been demonstrated to improve survival outcomes in patients with complicated invasive rhinosinusitis [*Chiang PT et al.,2022*].

The presence of EORTC host factors and the presence or number of non-traditional risk factors (such as diabetes, chronic kidney, chronic obstructive pulmonary, chronic liver, retroviral diseases,

TABLE 2.

Comparison of characteristics between patients who survived and those who died among patients with invasive pulmonary aspergillosis (N=42).

Characteristics	*Total (42)*	*Survived (30)*	*Expired (12)*	*p value*
Demographic features				
Age(mean±SD)	53.83±13.86	55.1±13.8	50.6±14.05	0.666
Male gender	30 (71.4%)	22(73.3%)	8(66.7%)	0.365
Co-morbidities				
Co morbidities	26(61.9%)	20(66.7%)	6(50%)	0.315
Nil co morbidities	11(26.2%)	7(23.3%)	4(33.3%)	0.505
Diabetes	16 (38.1%)	13(43.3%)	3(25%)	0.269
Retroviral disease	5(11.9%)	4(13.3%)	1(8.3%)	0.651
Hematological malignancy	3(7.1%)	2(6.7%)	1(8.3%)	0.85
Solid organ malignancy	2(4.8%)	1(3.3%)	1(8.3%)	0.492
Chronic kidney disease	7(16.7%)	4(13.3%)	3(25%)	0.359
Chronic obstructive pulmonary disease	5(11%)	5(16.7%)	-	0.132
Chronic liver disease	3(7.1%)	3(10%)	-	0.256
Prolonged steroid use	3(7.1%)	2(6.7%)	1(8.3%)	0.85
Otherimmunosuppressants	6(14.3%)	4(13.3%)	2(16.7%)	0.78
Short duration steroid	19(45.2%)	12(40%)	7(58.3%)	0.499
Viral pneumonia	12(28.6%)	6(20%)	6(50%)	0.069
EORTC host factors	7(16.7%)	4(13.3%)	3 (25%)	0.359
Clinical features				
Persistent fever	23(54.8%)	17(56.7%)	6(50%)	0.695
Dyspnoea	25(59.5%)	20(66.7%)	5(41.7%)	0.136
Haemoptysis	3(7.1%)	3(10%)	-	0.256
Chest pain	4(9.5%)	4(13.3%)	-	0.184
New onset or worsening respiratory supports	17 (40.5%)	6(20%)	11(91.7%)	**0.001***
Laborotary findings				
Culture positive	13(31%)	9(30%)	4(33.3%)	0.258
Histopathology positive	2(4.8%)	1(3.3%)	1(8.3%)	0.653
Serum Galactomannan	35(83.3%)	23(76.7%)	12(100%)	0.186
Neutropenia	5(11.9%)	3(10%)	2(16.7%)	0.449
Radiological findings				
Computed tomography findings (any)	33(78.6%)	24(80%)	9(75.0%)	0.721
Typical findings	14(33.3%)	9(30.0%)	5(41.7%)	0.614
Atypical findings	19(45.2%)	15(50%)	4(33.3%)	0.614
Treatment				
Amphotericin	1(2.4%)	1(3.3%)	-	0.101
Itraconazole	8(19%)	8(26.7%)	-	0.101
Voriconazole	33(78.6%)	21(70%)	12(100%)	0.101
Intensive care unit data				
Inotrope requirement	14(33.3%)	2(6.7%)	12(100%)	**0.001***
Invasive mechanical ventilation	15(35.7%)	3(10%)	12(100%)	**0.001***
Intensive care unit stay	26(61.9%)	14(46.7%)	12(100%)	**0.001***
Duration of Intensive care unit stay	10 ±6.97	7.29 ±4.64	13.17 ±8.03	**0.029***
Onset of acute kidney injury and worsening of acute kidney injury	11(26.2%)	4(13.3%)	7(58.3%)	**0.003***

NOTES: *(*) -P < 0.05 was considered statistically.*

or steroid treatment) did not significantly affect mortality in our study, which is consistent with findings from other studies [*Vandewoude K et al.,2004*; *Raveendran S et al.,2018*]. In contrast, other studies reported different results [*Sun KS et al.,2017*; *Faramakiotis D et al.,2019*].

In our study, no deaths occurred in chronic obstructive pulmonary or chronic liver disease patients with invasive aspergillosis, which contrasts with studies performed by Mir T with co authors and Falcone with co authors . This may be attributed to the selection criteria applied or low degree of clinical suspicion, leading to failure to perform the necessary diagnostic tests [*Falcone M et al, 2011; Mir T et al, 2022*]. Our findings contrast with those of a large retrospective study by Mir T with co authors, where chronic obstructive pulmonary disease patients with invasive aspergillosis had higher mortality and complication rates. Importantly, this group of patients had higher rates of lung malignancy, hematological malignancy, or a history of transplantation that were twice those of the non-aspergillosis chronic obstructive pulmonary disease patients.

Viral pneumonia weakens the respiratory system's natural defenses by damaging the airway lining, triggering excessive inflammation, and impairing the ability of immune cells, such as neutrophils and alveolar macrophages, to produce reactive oxygen species (ROS) through the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system. These reactive oxygen species play a key role in killing inhaled fungal spores. The resulting immune dysfunction not only facilitates fungal invasion but also predisposes to severe disease and hematogenous dissemination, including to critical sites like the brain [*Sampley S et al.,2022*]. Reported mortality rates in patients with viral pneumonia developing invasive pulmonary aspergillosis are high, ranging from 42% to 71% across multiple studies. Similarly, in our study, patients with viral pneumonia (COVID-19-associated pulmonary aspergillosis and Influenza-associated pulmonary aspergillosis) had notably higher ICU admission rates (13/14) (p = 0.003) and increased mortality (50%) (6/12, complete case analysis). Although not statistically significant (p=0.069), the trend suggests a strong association with poorer outcomes [*Schauwvlieghe A et al., 2018*; *Prattes J et al.,2022*].

Aspergillus fumigatus was the frequently isolated species (n = 9, 47.3%) in our study, similar to studies conducted by *Ebner J with co-authors*, but is not significantly associated with mortality [*Ebner J et al.,2022*]. The levels of galactomannan are considered to vary depending on the host, as circulating neutrophils clear antigens from the blood, which may result in lower levels in non-neutropenic patients [*Wu Z et al.,2021*]. Both serum and bronchoalveolar lavage galactomannan assays have varying sensitivities and specificities depending on the patient population [*Dobias R et al.,2018; Faramakiotis D et al.,2019*]. Elevated galactomannan levels indicate a greater Aspergillus burden, which increases the risk of dissemination as the fungus invades blood vessels, leading to increased mortality [*Prattes J et al.,2022*]. In our study population (n=51), a complete case analysis showed that serum galactomannan levels were positively correlated with mortality (p=0.037), which is consistent with the findings of *Fisher C* with co authors [*Fisher C et al., 2013*].

Although diagnostic bronchoscopy has been widely associated with accurately identifying invasive aspergillosis, it presents significant challenges due to safety concerns, particularly in COVID-19 patients, and difficulties performing the procedure on those requiring high ventilatory support or experiencing hemodynamic instability. In such cases, imaging, particularly high-resolution computerized tomography (CT), is crucial for diagnosing invasive aspergillosis in its early stages [*Raveendran S et al.,2018*]. and plays a key role in guiding the management of patients with suspected IPA [*Koehler P et al., 2019*] observed a correlation between CT findings and mortality in their study. However, in our study, we found no significant correlation between CT findings and mortality, which aligns with the findings of Horger M with co-authors [*Horger M et al., 2005*].

Voriconazole was found to be a superior antifungal in the treatment of invasive aspergillosis in a randomized control trial [*Herbrecht R et al.,2002*], which contrasts with our study, where all deaths occurred in patients receiving voriconazole. This observation does not imply a causal relationship and should be interpreted cautiously. The high mortality rate may be influenced by the fact that voriconazole was used in most cases

(80.3%, or 45 patients), possibly reflecting a preference for its use in more severely ill individuals. Furthermore, the absence of antifungal susceptibility testing at our center limits our ability to evaluate potential resistance, which has been linked to treatment failure and increased mortality in other studies [*Lestrade P et al.,2019*].

Among patients with IPA, a complete case analysis of ICU data showed that new-onset or worsening respiratory failure (p=0.001), inotropic requirements (p=0.001), new-onset or worsening acute kidney injury (p=0.003), the requirement for invasive mechanical ventilation (p=0.001), and duration of ICU stay (p=0.026) were positively correlated with mortality, which is consistent with findings from other studies [*Sun K et al.,2017; Faramakiotis D et al.,2019; Koehler P et al., 2019*]. A complete case analysis of the study population identified hemodynamic instability requiring inotropic support as an independent predictor of mortality on multivariate analysis, similar to the results reported by *Faramakiotis D with co-authors* [*Farmakiotis D et al., 2019*].

Limitations: The main limitations of our study were primarily its retrospective design and modest sample size. Although BM-AspICU showed a better correlation with mortality, this finding requires confirmation through prospective studies. The application of ICU-specific diagnostic frameworks, such as the BM-AspICU criteria, to non-ICU populations has not been formally validated and may affect the generalizability of our findings. Additionally, as a retrospective study, we could not obtain galactomannan optical density index values, so we categorized all cases based on positive results. The unavailability of drug sensitivity testing may have influenced treatment decisions and impacted mortality.

Conclusion

In our study, the BM-AspICU criteria showed a stronger association with mortality, highlighting its potential as a more effective tool for classifying IPA in ICU patients. However, its applicability in medical ward settings remains to be further assessed and validated. The findings also emphasize the critical role of antifungal susceptibility testing and the early identification of high-risk patients. Notably, we found that viral pneumonia, elevated serum galactomannan levels, respiratory failure requiring invasive mechanical ventilation, shock, renal failure, and extended ICU stays were significantly linked to increased morbidity and mortality.

Clinical significance: This study highlights the limitations of conventional diagnostic criteria in detecting invasive pulmonary aspergillosis among critically ill patients. The application of the BM-AspICU algorithm may enhance diagnostic accuracy and enable earlier antifungal intervention. Although voriconazole is generally considered effective for invasive aspergillosis, its association with high mortality in this study highlights the need for antifungal susceptibility testing to guide appropriate therapy. Notably, the presence of shock requiring inotropic support was identified as an independent predictor of mortality, highlighting the critical need for prompt recognition and intervention. These findings advocate for updated diagnostic approaches and risk stratification tools to guide therapy better and reduce mortality in critically ill patients.

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Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37493) 588697 Editor-in-Chief
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