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ORIGINAL RESEARCH

A Comparison of Diagnostic Criteria for Invasive Pulmonary Aspergillosis in Critically Ill Patients

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ABSTRACT

Introduction: Invasive pulmonary aspergillosis (IPA) is a common infection in intensive care units (ICUs). There are no consensus criteria for defining IPA in the ICU. We aimed to compare the diagnosis and prognosis performances of three criteria (the 2020 EORTC/MSG criteria, the 2021 EORTC/MSG ICU criteria, the modified AspICU criteria (M-AspICU)) for IPA in the ICU.

Methods: In this retrospective study from our single center, we applied the three different criteria for IPA in patients with suspected pneumonia and undergoing at least one mycological test between November 10, 2016 and November 10, 2021. We compared the diagnosis agreement and prognosis performances of these three criteria in the ICU.

Results: Overall, 2403 patients were included. The rates of IPA according to the 2020 EORTC/MSG, 2021 EORTC/MSG ICU, and M-AspICU were 3.37%, 6.53%, and 23.10%, respectively. Diagnostic agreement among these criteria was poor (Cohen's kappa 0.208–0.666). IPA diagnosed by either the 2020 EORTC/MSG (odds ratio = 2.709, $P < 0.001$) or the 2021 EORTC/MSG ICU (odds ratio = 2.086, $P = 0.001$) criteria was independently associated with 28-day mortality. IPA diagnosed by M-AspICU is an independent risk factor of 28-day mortality (odds ratio = 1.431, $P = 0.031$) when excluding patients who fulfilled neither host criteria nor radiological factors of 2021 EORTC/MSG ICU.

Conclusions: Although M-AspICU criteria have the highest "sensitivity", IPA diagnosed by M-AspICU was not an independent risk factor of 28-day mortality. Caution is required when using the M-AspICU criteria in ICU, especially in patients with non-specific infiltration and non-classical host factors.

Keywords: Invasive pulmonary aspergillosis; Intensive care unit; EORTC/MSG criteria; Modified AspICU criteria; Mortality; Diagnostic

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Key Summary Points

Why carry out this study?

Invasive pulmonary aspergillosis is a common infection in intensive care units. There are no consensus criteria for defining IPA in the ICU.

The study evaluated the diagnostic agreement and performance of latest three criteria (the 2020 EORTC/MSG, 2021 EORTC/MSG ICU, and M-AspICU) for diagnosing IPA in critically ill patients.

What was learned from the study?

The three criteria (the 2020 EORTC/MSG, 2021 EORTC/MSG ICU, and M-AspICU) for diagnosing IPA showed very poor diagnostic agreement.

IPA diagnosed by either the 2020 EORTC/MSG or the 2021 EORTC/MSG ICU criteria was independently associated with 28-day mortality. Although the M-AspICU criteria have the highest "sensitivity", IPA diagnosed by M-AspICU was not an independent risk factor of 28-day mortality.

Caution is required when using the M-AspICU criteria in ICU, especially in patients with non-specific infiltration and non-classical host factors.

INTRODUCTION

Invasive pulmonary aspergillosis (IPA), a common opportunistic infection in the intensive care unit (ICU), is associated with increased mortality [1–4]. The reported incidence of IPA among critically ill patients varies widely from 9.4% to 69% [2–5]. The significant differences in these values can be attributed to the lack of lung histopathology, heterogeneity among different types of ICU patients, and most importantly, the lack of consensus criteria on how to define IPA in the ICU population. Rapid and accurate diagnosis of IPA is critical for early administration of appropriate antifungal therapy and improved prognosis.

The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) first proposed diagnostic criteria for IPA in 2002 and updated these criteria in 2008 and 2020 for better use in research and clinical care [6–8]. However, these criteria are aimed primarily at immunocompromised populations. In 2021, EORTC/MSG proposed IPA criteria for the ICU population [9]. Blot et al. proposed a clinical algorithm for IPA (AspICU criteria) that relies on a positive *Aspergillus* culture in lower respiratory tract specimens (LRTs) and is used to differentiate infection from colonization [10]. Schauwvlieghe et al. modified the AspICU criteria (M-AspICU) with the purpose of improving low sensitivity to culture and ICU population inapplicability [3]. Both the EORTC/MSG and M-AspICU criteria classify patients with IPA as "proven" and "probable" (EORTC/MSG)/"putative" (M-AspICU) cases. "Proven" cases are only defined with positive lung histopathology results, but this invasive test is not suitable for ICU patients with severe respiratory failure, coagulation disorders, or other complications. The diagnosis of probable IPA, which relies on a combination of host factors, clinical symptoms, mycological findings, and radiological findings, is relatively non-invasive and thus more suitable for ICU patients. The updated EORTC/MSG and M-AspICU criteria focus on probable cases with enlargement of host factors and imaging results and the revision of mycological criteria to identify more IPA cases.

To date, only a few studies have compared different criteria for IPA diagnosis in critically ill patients. In this study, we compared the rates of IPA according to the 2020 EORTC/MSG, 2021 EORTC/MSG ICU, and M-AspICU criteria in an ICU population and evaluated the effects of the three different IPA criteria on patient outcomes.

METHODS

Study Design and Population

We conducted a retrospective single-center study in two ICUs (medical and surgical) of Peking Union Medical College Hospital between November 10, 2016 and November 10, 2021. Patients with the following characteristics were included: (1) age over 18 years; (2) length of ICU stay longer than 48 h; (3) had suspected pneumonia; (4) had any of the following tests done: Aspergillus galactomannan (GM) enzyme immunoassay test in serum or bronchoalveolar lavage fluid (BALF), LRT fungal culture (sputum, BALF, bronchial brush, or aspirate), or lung histopathology; (5) had a chest computed tomography (CT) examination, and the interval between CT and mycological test was less than 7 days.

Data Collection

The following variables were collected from patient records: age, gender, comorbidities, Acute Physiology and Chronic Health (APACHE II) score on admission, and Sequential Organ Failure Assessment (SOFA) score on the day of first retained GM; if the patient did not have a GM test, we selected the day of the first retained fungal culture of the LRTs. We also collected mycological tests, including fungal cultures of LRTs, serum GM, and BALF GM and chest CT data, and lung histopathology. Chest CT data were obtained by two senior ICU doctors who reviewed the chest images. If there were any disagreements, the two doctors had a discussion, and another senior ICU doctor was consulted if a consensus could not be reached. Finally, we collected invasive mechanical ventilation and survival status at 28 days.

Diagnostic Criteria

We selected three recent diagnostic criteria to diagnose IPA in critically ill patients: (1) the EORTC/MSG criteria published by Donnelly et al. in 2020 (2020 EORTC/MSG) [7]; (2) the EORTC/MSG ICU Working Group criteria published by Bassetti et al. in 2021 (2021 EORTC/MSG ICU) [9]; and (3) the algorithms published by Schauwvlieghe et al. in 2018 (M-AspICU) [3]. The detailed diagnostic criteria are listed in Supplementary Material 1. We defined "proven" and "probable" IPA as IPA cases, while "possible" IPA and cases that could not be classified by any of the diagnostic criteria were defined as patients without IPA ("No-IPA").

Statistical Analysis

Continuous variables are presented as mean with standard deviation or median with interquartile range and were compared by *t* test or Mann–Whitney *U* test, respectively. Categorical data are reported as proportions and compared using the chi-square test. Diagnostic agreement was calculated using Cohen's kappa. We performed a multivariate binary logistic regression analysis to detect independent risk factors of 28-day mortality and to assess the association of each criterion with 28-day mortality. $P < 0.05$ was considered significant. Data were analyzed using SPSS version 21.0.1. Figures were designed using Prism version 9.0.

Ethics Statement

The study was approved by the institutional review boards and Ethics Committee of Peking Union Medical College Hospital. As a result of the retrospective nature of the study, informed written consent was waived. The study was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

Study Population and Characteristics

A total of 2403 patients met the inclusion criteria between November 10, 2016 and November 10, 2021. (Supplementary Material 2). The patient characteristics are shown in Table 1. Of the 2403 patients, 1462 (60.8%) were male, and the mean age was 59 years. Almost one-third of

Table 1 Patient characteristics

Characteristic of patients (n = 2403)	
Mean age (SD), years	59 (17.1)
Male, n (%)	1462 (60.8)
Admission type, n (%)	
Medical admission	759 (31.6)
Surgical admission	1644 (68.4)
Severity of illness	
APACHE II score on ICU admission, median (IQR)	18 (13–22)
SOFA score, median (IQR)	7 (6–10)
IMV, n (%)	1376 (57.3)
Comorbidities, n (%)	
Diabetes mellitus	596 (24.8)
COPD	96 (4.0)
Liver cirrhosis	51 (2.1)
AKI	483 (20.1)
Influenza	50 (2.1)
Immune deficiency state	
Neutropenia[a]	79 (2.8)
Hematologic malignancy	120 (5.0)
Solid tumor	227 (9.4)
Solid organ transplant	24 (4.9)
Glucocorticoid[b]	261 (10.9)
Mycological findings	
Performed serum GM, n (%)	2286 (95.1)
Serum GM $\leq$ 0.5	1880 (78.2)
0.5 < serum GM $\leq$ 1.0	309 (12.9)
Serum GM > 1.0	97 (4.0)
Serum GM, median (IQR)	0.25 (0.17–0.44)
Performed BALF GM, n (%)	315 (13.1)
BALF GM $\leq$ 0.8	195 (8.1)
0.8 < BALF GM $\leq$ 1.0	17 (0.7)
BALF GM > 1.0	103 (4.3)
BALF GM, median (IQR)	0.32 (0.25–1.91)
Performed fungal culture, n (%)	2403 (100)
Positive fungal culture, n (%)	208 (8.7)
Radiological findings n (%)	
Nodule	167 (6.9)
Cavity	83 (3.5)
Consolidation	451 (18.8)
Other infiltrates	1834 (76.3)

ICU intensive care unit, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *IMV* invasive mechanical ventilation, *COPD* chronic obstructive pulmonary disease, *AKI* acute kidney injury, *GM* galactomannan, *BALF* bronchoalveolar lavage fluid

[a]Present on the day of BALF and/or first sample of culture

[b]Glucocorticoid treatment with prednisone equivalent of 20 mg or more per day during the past 90 days

the patients were admitted to the ICU for medical conditions. The patients in our study had a median APACHE II score of 18, of whom 1376 (57.3%) required invasive mechanical ventilation. None of the patients had lung histopathology, but all had fungal cultures in LRTs. Serum GM tests were performed in 2286 (95.1%) patients, and 315 also underwent BALF GM testing.

IPA Diagnostic Rates

The frequency of IPA varied substantially among the three criteria. According to the 2020 EORTC/MSG, 2021 EORTC/MSG ICU, and M-AspICU criteria, IPA was present in 81 (3.37%), 157 (6.53%), and 555 (23.10%) cases, respectively. Patients with IPA diagnosed according to the 2020 EORTC/MSG also met 2021 EORTC/MSG ICU criteria, while patients with IPA diagnosed according to the 2021 EORTC/MSG ICU also met the M-AspICU

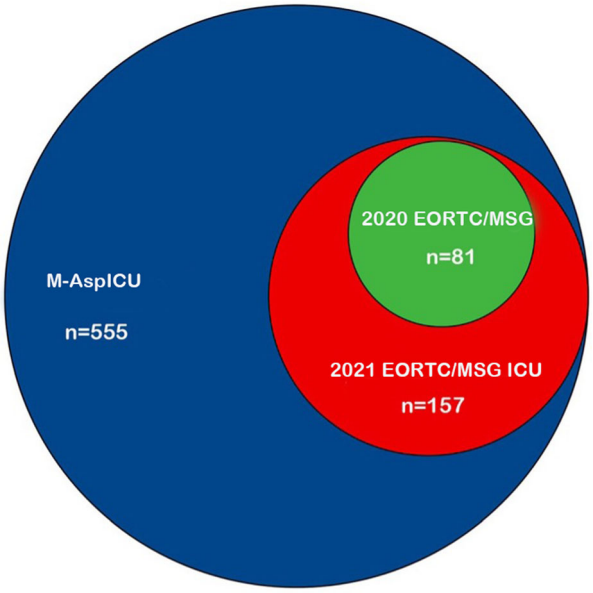


Fig. 1 The distribution of invasive pulmonary aspergillosis by single criteria and the overlap of three diagnostic criteria in all patients

criteria (Fig. 1). The characteristics of patients with IPA diagnosed using the three criteria are shown in Table 2. Compared to the M-AspICU, the 2020 EORTC/MSG and 2021 EORTC/MSG ICU criteria diagnosed more severely ill patients. There were no differences in serum GM and BALF GM among patients with IPA diagnosed by the three criteria. Patients with IPA diagnosed by the 2020 EORTC/MSG had the highest rate of positive *Aspergillus* culture (71.6%), while patients diagnosed using the M-AspICU had the lowest rate (37.5%).

Diagnostic Agreement Among the Three Criteria

The diagnostic agreement between the three diagnostic criteria was poor, with a Cohen's kappa of only 0.328 ($P < 0.001$). The diagnostic agreements between any two of the three criteria are shown in Fig. 2.

2021 EORTC/MSG ICU Criteria vs. 2020 EORTC/MSG Criteria

Compared with the 2020 EORTC/MSG criteria, the 2021 EORTC/MSG ICU criteria diagnosed 76 additional patients with IPA. Among these patients, 37 (48.7%) were diagnosed because of the broader host criteria alone, which included chronic obstructive pulmonary disease (COPD; $n = 20$), severe influenza ($n = 12$), and decompensated liver cirrhosis ($n = 10$), 29 (38.2%) were diagnosed because of the lower serum GM positive threshold alone, with a median of 0.59 (0.41–0.71), and 10 (13.1%) were diagnosed owing to a combination of both.

2021 EORTC/MSG ICU Criteria vs. M-AspICU Criteria

Compared with the 2021 EORTC/MSG ICU criteria, the M-AspICU criteria diagnosed 398 additional patients with IPA. Among them, 154 (38.7%) were diagnosed because of broader host factors alone, which included solid tumors ($n = 28$), diabetes mellitus ($n = 57$), acute kidney injury ($n = 66$), 119 (29.9%) patients were diagnosed because of the broader radiological factors alone, and the remaining 125 (31.4%) patients were diagnosed owing to both of the above. Although the BALF GM threshold is higher for the M-AspICU criteria (1.0) than for the 2021 EORTC/MSG ICU criteria (0.8), this small difference had no effect on IPA diagnosis in our study.

Outcomes of IPA Diagnosed Using the Three Criteria

Compared to those without IPA, 28-day mortality was significantly higher in patients with IPA, regardless of the criteria used: 2020 EORTC/MSG criteria (40.7% vs. 11.4%, $P < 0.001$); 2021 EORTC/MSG ICU criteria (34.4% vs. 10.6%, $P < 0.001$); and M-AspICU criteria (19.8% vs. 9.9%, $P < 0.001$).

2021 EORTC/MSG ICU Criteria vs. 2020 EORTC/MSG Criteria

There was no difference in 28-day mortality between patients with IPA diagnosed using the 2021 EORTC/MSG ICU and 2020 EORTC/MSG criteria (34.4% vs. 40.7%, $P = 0.335$) (Fig. 3). Patients diagnosed by the 2021 EORTC/MSG ICU criteria but missed by the 2020 EORTC/MSG criteria had higher 28-day mortality than

Table 2 Characteristics and clinical outcomes of patients classified as IPA according to the three criteria

	IPA according to 2020 EORTC/MSG (*n* = 81)	IPA according to 2021 EORTC/MSG ICU (*n* = 157)	IPA according to M-AspICU (*n* = 555)	*P* value
Mean age (SD), years	56 (16.4)	58 (16.1)	58 (17.5)	0.263
Male, *n* (%)	41 (50.6)	92 (59.0)	320 (57.7)	0.448
Admission type, *n* (%)				
Medical admission	62 (76.5) †‡	98 (62.4)*‡	264 (47.6)*†	< 0.001
Surgical admission	19 (23.5) †‡	59 (37.6)*‡	291 (52.4)*†	< 0.001
Severity of illness				
APACHE II score on ICU admission, median (IQR)	22 (17–29)‡	21 (16–26)‡	19 (15–25)*†	0.001
SOFA score, median (IQR)	9 (7–13)‡	9 (6–13)	8 (6–11)*	0.009
IMV, *n* (%)	66 (81.5)‡	129 (82.2)‡	386 (69.5)*†	0.002
Comorbidities, *n* (%)				
Diabetes mellitus	13 (16.0)‡	24 (15.3)‡	153 (27.6)*†	0.001
COPD	5 (6.2)†	34 (21.7)*‡	46 (8.3)†	< 0.001
Liver cirrhosis	1 (1.2)†	16 (10.2)*‡	24 (4.3)†	0.003
AKI	40 (49.4)	77 (49.0)‡	220 (39.6)†	0.045
Influenza	10 (12.3)‡	23 (14.6)‡	27 (4.9)*†	< 0.001
Immune deficiency state				
Neutropenia[a]	21 (25.9)†‡	25 (15.9)*‡	51 (9.2)*†	< 0.001
Hematologic malignancy	18 (22.2) ‡	23 (14.7) ‡	46 (8.3)*†	< 0.001
Solid tumor	2 (2.5)‡	7 (4.5)‡	58 (10.5)*†	0.007
Solid organ transplant	8 (9.9)‡	11 (7.1)‡	14 (2.5)*†	0.001
HIV	0 (0)	0 (0)	4 (0.7)	0.422
Glucocorticoid[b]	55 (67.9)†‡	72 (45.9)*‡	142 (25.6)*†	< 0.001
Mycological findings				
GM in serum, median (IQR)	0.56 (0.34–1.21)	0.59 (0.36–0.82)	0.61 (0.51–0.86)	0.288
GM in BALF, median (IQR)	4.05 (1.01–5.00)	4.35 (1.04–5.00)	3.34 (0.95–5.00)	0.759
Positive fungal culture, *n* (%)	58 (71.6)†‡	84 (53.5)*‡	208 (37.5)*†	< 0.001
Radiological findings *n* (%)				

Table 2 continued

	IPA according to 2020 EORTC/MSG (*n* = 81)	IPA according to 2021 EORTC/MSG ICU (*n* = 157)	IPA according to M-AspICU (*n* = 555)	*P* value
Nodule	23 (28.4)‡	42 (26.8)‡	81 (14.6)*†	< 0.001
Cavity	17 (21.0)‡	29 (18.5)‡	50 (9.0)*†	< 0.001
Consolidation	62 (76.5)‡	121 (77.1)‡	252 (45.4)*†	< 0.001
Clinical outcome				
Length of stay in ICU, median (IQR), days	10 (5–20)	10 (5–21)	9 (4–19)	0.312
ICU mortality, *n* (%)	37 (45.7)‡	61 (38.9)‡	125 (22.5)*†	< 0.001
28-day mortality, *n* (%)	33 (40.7)‡	54 (34.4)‡	110 (19.8)*†	< 0.001

EORTC/MSG Criteria for IPA by The European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group

IPA invasive pulmonary aspergillosis, *ICU* intensive care unit, *M-AspICU* modified algorithm for IPA in ICU, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *IMV* invasive mechanical ventilation, *HIV* human immunodeficiency virus, *COPD* chronic obstructive pulmonary disease, *GM* galactomannan, *BALF* bronchoalveolar lavage fluid

[a]Present on the day of BALF and/or first sample of culture

[b]Glucocorticoid treatment with prednisone equivalent of 20 mg or more per day during the past 90 days

*$P < 0.05$, compared with IPA according to 2020 EORTC/MSG

†$P < 0.05$, compared with IPA according to 2021 EORTC/MSG ICU

‡$P < 0.05$, compared with IPA according to M-AspICU

patients without IPA based on the 2021 EORTC/MSG ICU criteria (27.6% vs. 10.6%, $P < 0.001$). The 28-day mortality rates of the additional patients diagnosed by the 2021 EORTC/MSG ICU criteria (as a result of broader host factors, lower GM threshold, or both) were higher than the patients without IPA based on the EORTC-ICU criteria (Supplementary Material 3).

2021 EORTC/MSG ICU Criteria vs. M-AspICU Criteria

The 28-day mortality rate of patients with IPA diagnosed by the M-AspICU criteria was lower than that of patients diagnosed by the 2021 EORTC/MSG ICU criteria (19.8% vs. 34.4%, $P < 0.001$) (Fig. 3). Patients diagnosed with IPA using the M-AspICU criteria but missed by the 2021 EORTC/MSG ICU criteria had higher 28-day mortality than patients without IPA based on the M-AspICU criteria (14.1% vs. 9.9%, $P = 0.014$). The 28-day mortality rate of the additional patients diagnosed by the M-AspICU criteria as a result of either broader host factors or broader radiological factors alone was higher than patients without IPA based on the M-AspICU criteria. However, the 28-day mortality rate of additional patients diagnosed by the M-AspICU criteria owing to both broader host factors and broader radiological factors was similar to patients without IPA based on M-AspICU criteria (8.8% vs. 9.9%, $P = 0.689$) (Supplementary Material 3).

Predictive Ability of the Three Criteria for Mortality

IPA diagnosed by the 2020 EORTC/MSG or 2021 EORTC/MSG ICU criteria was independently associated with 28-day mortality, even after adjustment for intensive mechanical

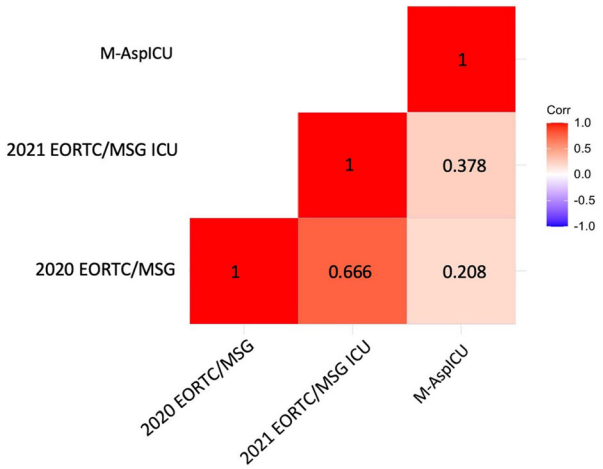


Fig. 2 Cohen's kappa correlation between any of the three criteria

ventilation, acute kidney injury, and SOFA score (Fig. 4). IPA diagnosed by the M-AspICU criteria is an independent risk factor of 28-day mortality [odds ratio (OR) = 1.431, 95% confidence interval (CI) = 1.034–1.981, $P = 0.031$] only when excluding patients who fulfilled neither the host factors nor radiological features of 2021 EORTC/MSG ICU.

DISCUSSION

We compared the diagnostic and prognostic performance of the 2020 EORTC/MSG, 2021 EORTC/MSG ICU, and M-AspICU criteria for IPA in an ICU population. The main findings of our study can be summarized as follows: (1) the diagnostic rate of IPA in the ICU population ranged from 3.34% based on the 2020 EORTC/MSG criteria to 23.1% based on the M-Asp ICU criteria; (2) IPA diagnosed by either the 2020 EORTC/MSG or 2021 EORTC/MSG ICU criteria was independently associated with 28-day mortality; (3) IPA diagnosed by the M-AspICU criteria is an independent risk factor of 28-day mortality when excluding patients who fulfilled neither the host factors nor radiological features of 2021 EORTC/MSG ICU.

The diagnostic rate of IPA according to the M-AspICU criteria was four times higher than that based on the 2021 EORTC/MSG ICU criteria. These findings are in alignment with the results of Schroeder et al., who compared the two criteria in critically ill patients with positive LRT *Aspergillus* cultures (Cohen's kappa = 0.12) [11]. The poor diagnostic agreement between the 2020 EORTC/MSG and M-AspICU criteria was similar to the results of Szabo et al.'s study of patients with corona virus disease 2019 (COVID-19) (Cohen's kappa = 0.154) [12].

The 2020 EORTC/MSG criteria are not suitable for ICU patients because they only can identify patients with hematological malignancies and severe immunosuppression. Patients with IPA would be missed in the ICU according to the 2020 EORTC/MSG criteria. To reduce the likelihood of missing IPA diagnoses in the ICU, the diagnostic criteria were broadened. Compared with the 2020 EORTC/MSG criteria, additional host factors including influenza and COPD were added to the 2021 EORTC/MSG ICU criteria, and the positive threshold for serum GM was decreased from 1.0 to 0.5. Schauwvlieghe et al. concluded that influenza was independently associated with IPA [3]. An autopsy of 67 patients with proven IPA indicated that half had underlying diseases with COPD [13]. According to our findings, the use of the 2021 EORTC/MSG ICU criteria increased the rate of IPA diagnosis by 48.4% compared with the 2020 EORTC/MSG criteria. Among the additional patients diagnosed with IPA using the 2021 EORTC/MSG ICU criteria, those diagnosed because of expanded host factors alone had higher mortality than patients without IPA. Similarly, those diagnosed because of the lower GM threshold also had higher mortality than those without IPA. These findings support the diagnostic value of the 2021 EORTC/MSG ICU criteria in the ICU setting.

The 2021 EORTC/MSG ICU criteria add COPD and influenza in addition to the classic host factors. ICU patients with diabetes, solid tumors, and other underlying conditions, on the other hand, are susceptible to IPA [14, 15]. We may require broader IPA criteria for ICU patients. Compared to the 2021 EORTC/MSG ICU criteria, the M-AspICU criteria further broaden the diagnostic criteria with no host factor limitations and any infiltrates on lung

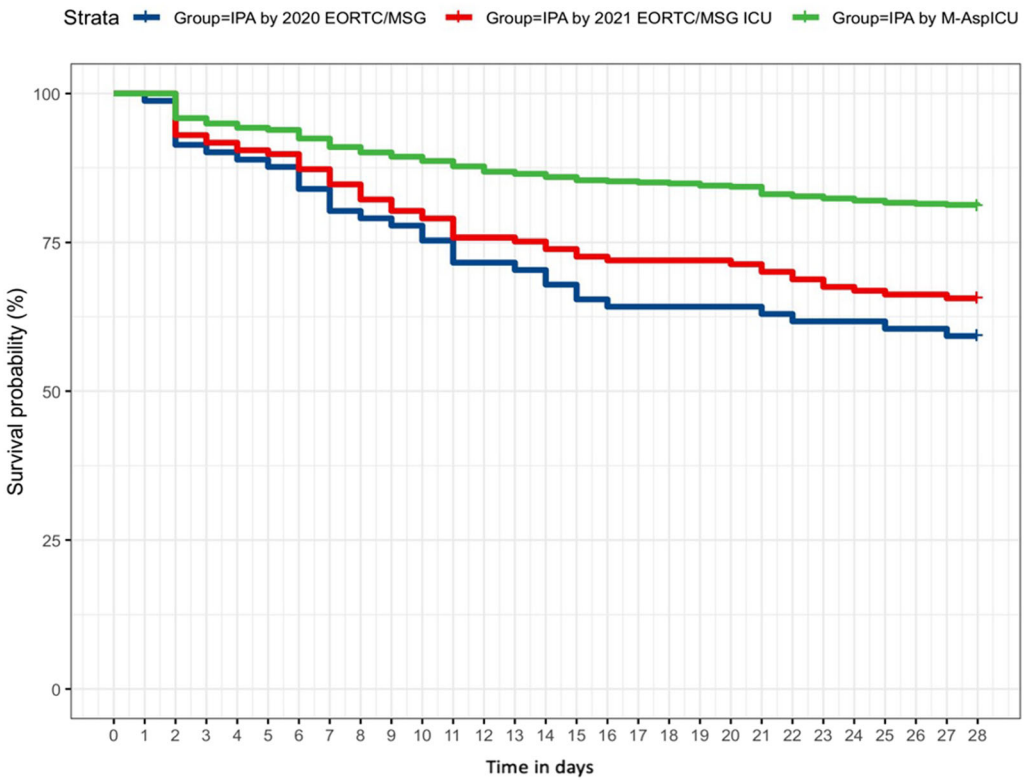
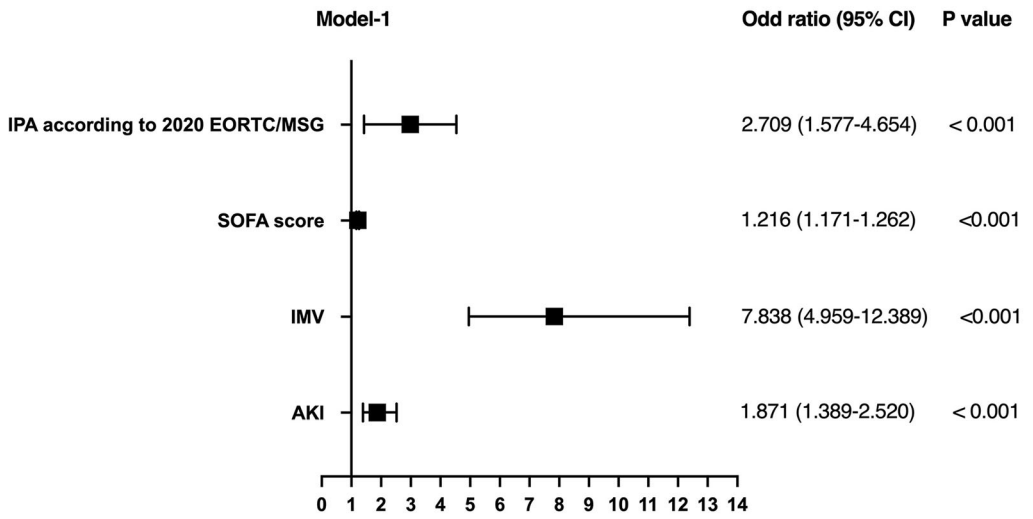


Fig. 3 Kaplan–Meier for 28-day survival of patients with IPA

imaging. The M-AspICU criteria diagnosed more than three times as many patients with IPA in this study. These patients with IPA had higher mortality than patients without IPA based on the M-AspICU criteria. More than one-third of the patients were diagnosed with IPA using the M-AspICU as a result of the broadened host factors alone. Among them, 37% had DM, and 19% had solid tumors. Several studies have supported diabetes mellitus (DM) and solid tumors as risk factors for IPA in critically ill patients. This finding is consistent with the results of Taccone et al., who found that either DM or solid tumors were present in nearly 20% of patients with proven IPA [16]. Cornillet et al. reported that ground-glass opacities and pleural effusions were more common in ICU patients with IPA [14]. Huang et al. demonstrated that patchiness was the most common CT sign among critically ill patients with both IPA and COPD [17]. In the present study, nearly one-third of the patients that were diagnosed with IPA using the M-AspICU criteria but missed by the 2021 EORTC/MSG ICU criteria as a result of non-specific infiltration alone had higher mortality than patients without IPA.

Although the M-AspICU criteria diagnosed the largest cohort of patients with IPA among the three criteria, IPA based on the criteria was not an independent risk factor of mortality. Schroder et al. found a high false positive rate of IPA (up to 71%) based on M-AspICU criteria in patients with proven IPA [11]. In the present study, we found that the subgroup of additional patients diagnosed by the M-AspICU criteria owing to both the expanded host factors and radiological features had a low mortality rate that did not differ from the rate among patients without IPA. Although all of these patients met the mycological criteria, *Aspergillus* colonization and false positives should be considered. After we excluded these additional patients mentioned above, IPA diagnosed by M-AspICU became an independent risk factor of 28-day mortality. Thus, the clinical significance of this


Model-1
Odd ratio (95% CI)
P value
IPA according to 2020 EORTC/MSG
2.709 (1.577-4.654)
< 0.001
SOFA score
1.216 (1.171-1.262)
<0.001
IMV
7.838 (4.959-12.389)
<0.001
AKI
1.871 (1.389-2.520)
< 0.001
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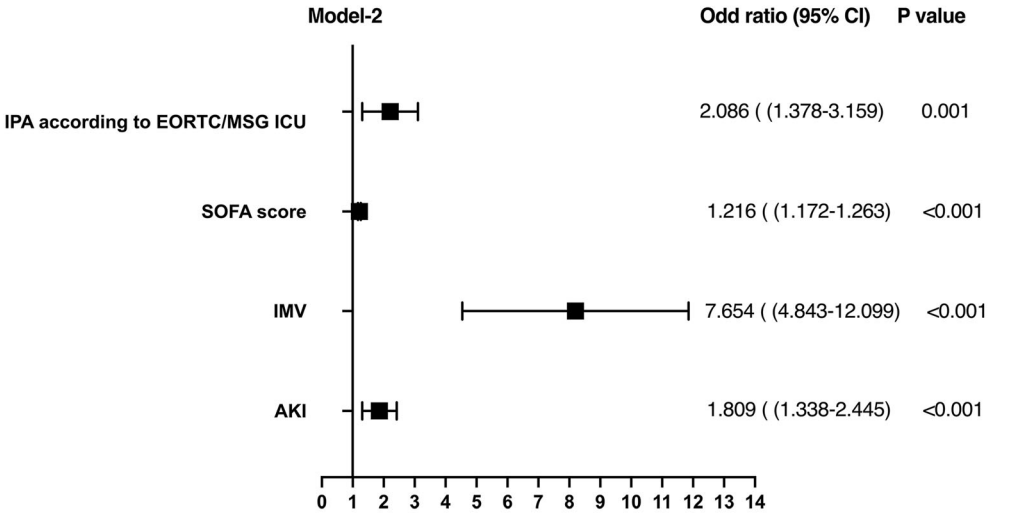
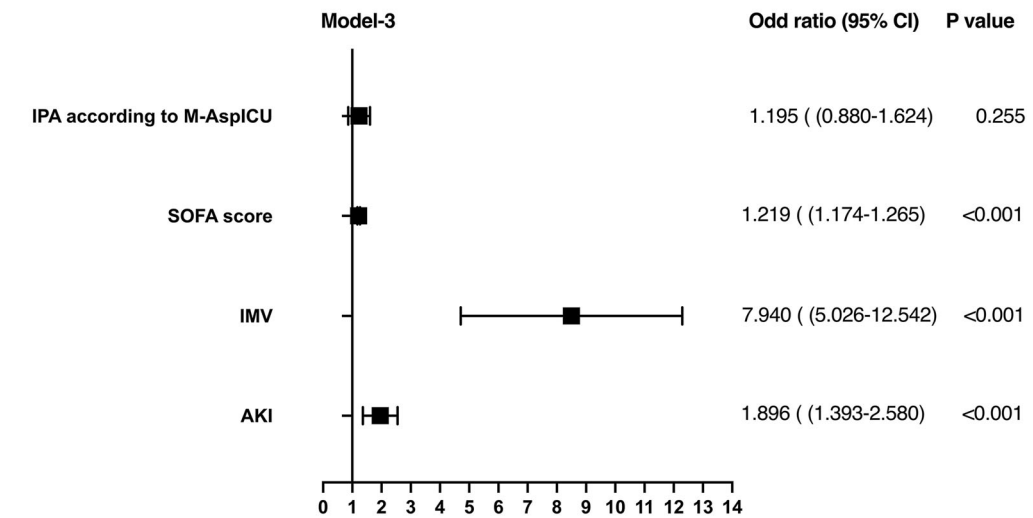

Model-2
Odd ratio (95% CI)
P value
IPA according to EORTC/MSG ICU
2.086 ((1.378-3.159)
0.001
SOFA score
1.216 ((1.172-1.263)
<0.001
IMV
7.654 ((4.843-12.099)
<0.001
AKI
1.809 ((1.338-2.445)
<0.001
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14


Model-3
Odd ratio (95% CI)
P value
IPA according to M-AspICU
1.195 ((0.880-1.624)
0.255
SOFA score
1.219 ((1.174-1.265)
<0.001
IMV
7.940 ((5.026-12.542)
<0.001
AKI
1.896 ((1.393-2.580)
<0.001
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

◀**Fig. 4** Forest plots of risk factors for 28-day mortality. Model 1: Analysis of risk factors based on the model includes IPA diagnosed by the 2020 EORTC/MSG criteria and other univariable factors. Model 2: Analysis risk factors based on the model includes IPA diagnosed by the 2021 EORTC/MSG ICU criteria and other univariable factors. Model 3: Analysis of risk factors based on the model includes IPA diagnosed by the M-AspICU criteria and other univariable factors. Displayed are only those variables that remained in the model during variable selection. OR odds ratio, DM diabetes mellitus, IMV invasive mechanical ventilation, SOFA Sequential Organ Failure Assessment, IPA invasive pulmonary aspergillosis, EORTC/MSG Consensus Definitions of IPA from European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group, M-AspICU modified algorithm for IPA

subgroup of patients warrants further evaluation.

Our study has some limitations. First, all patients did not have lung histopathology. Second, the 2020 EORTC/MSG criteria included *Aspergillus* PCR; however, this technique is not available in our hospital, which may have caused us to underestimate the actual diagnostic rate of the 2020 EORTC/MSG criteria. Siopi et al. confirmed that cases of probable IPA increased by 22% when PCR was used [18]. Third, there were no patients with COVID-19 in our study. Although the inclusion dates from November 2016 to November 2021, our hospital is not a designated hospital for COVID-19 patients. However, there are other influenza data in our study. Fourth, BALF GM is more valuable than serum GM for diagnosing IPA in the ICU population [2, 19]. However, only 13.1% of patients in our study had BALF GM. Fifth, this was a single-center study, and the results may be biased; finally, radiologic features other than nodes, cavities, and consolidation were not collected.

CONCLUSION

The diagnostic rate of IPA in critically ill patients varied considerably based on the diagnostic criteria used, with very poor agreement between the three evaluated criteria. Compared with the 2020 EORTC/MSG criteria, the 2021 EORTC/MSG ICU criteria identified a group of patients with similarly devastating outcomes. Although the M-AspICU criteria have the highest sensitivity since they identify most patients as "probable" given the broadened criteria, this study shows that these patients are less ill. Whether broadened host factors and/or broadened radiologic features should be incorporated into the diagnostic criteria should be further evaluated in prospective cohort studies.

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Authors' Contributions. Bin Du and Ruiting Liu designed the study. Shan Li, Yan Chen and Xi-xi Wan interpreted the clinical data. Jinmin Peng and Li Weng directed the writing. The first draft of the manuscript was written by Ruiting Liu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosures. Rui-ting Liu, Yan Chen, Shan Li, Xi-xi Wan, Li Weng, Jin-min Peng and Bin Du declare that they have no conflicts of interest to this work.

Compliance with Ethics Guidelines. The study was approved by the institutional review boards and Ethics Committee of Peking Union Medical College Hospital. As a result of the retrospective nature of the study, informed

written consent was waived. The study was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Data Availability. The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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