

# **A comparison of diagnostic criteria for invasive pulmonary aspergillosis in critically ill patients**

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## Supplementary Material 1: Brief descriptions of each diagnostic criteria for probable IPA

|                      | 2020 EORTC/MSG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 2021 EORTC/MSG ICU                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | M-AspICU                                                  |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| <b>Host factors</b>  | 1.Recent history of neutropenia ( $<0.5 \times 10^9/L$ for more than 10 days) temporally related to the onset of fungal disease.<br>2.Prolonged use of corticosteroids at a therapeutic dose of $\geq 0.3$ mg/kg corticosteroids for $\geq 3$ weeks in the past 60 days<br>3. Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor- $\alpha$ blockers, lymphocyte-specific monoclonal antibodies, immunosuppressive nucleoside analogues during the past 90 days<br>4.Hematological malignancy/ Receipt of an allogeneic stem cell transplant.<br>5.Receipt of a solid organ transplant<br>6. Acute graft-versus-host disease grade III or IV involving the gut, lungs or liver that is refractory to first-line treatment with steroids<br>7. Inherited severe immunodeficiency.<br>8.Treatment with recognized B-cell immunosuppressants | 1. Qualitative or quantitative neutrophil abnormality (inherited neutrophil deficiency, absolute neutrophil count of $\leq 500$<br>2. Glucocorticoid treatment with prednisone equivalent of 20 mg or more per day cells/mm <sup>3</sup> )<br>3. Treatment with recognized immunosuppressants during the past 90 days<br>4. Hematological malignancies/HSCT<br>5. SOT<br>6. Human immunodeficiency virus infection<br>7.Chronic respiratory airway abnormality (chronic obstructive lung disease, bronchiectasis)<br>8.Decompensated cirrhosis<br>9. Severe influenza (or other severe viral pneumonia, such as coronavirus disease 2019 [COVID-19])<br>10.ICU patients | ICU patients                                              |
| <b>Clinical Data</b> | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | One of the following signs or symptoms had to be present: |

|                              |                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              |                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                       | 1. Fever refractory to at least 3 days of appropriate antibiotic therapy.<br>2. Recrudescence of fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause.<br>3. Dyspnoea.<br>4. Haemoptysis.<br>5. Pleural friction rub or chest pain.<br>6. Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support. |
| <b>Radiological findings</b> | The presence of 1 of the following 4 signs on CT:<br>1. Dense, well-circumscribed lesion(s) with or without a halo sign.<br>2. An air-crescent sign.<br>3. A cavity.<br>4. Wedge-shaped and segmental or lobar consolidation                                                                                                                                                                          | The presence of 1 of the following 4 signs on CT:<br>1. Dense, well-circumscribed lesions with or without a halo sign<br>2. Air crescent sign<br>3. Cavity<br>4. Wedge-shaped and segmental or lobar consolidation                                                                    | Any infiltrate on pulmonary imaging by portable chest x-ray or CT scan of the lungs.                                                                                                                                                                                                                                                                                                                            |
| <b>Mycological findings</b>  | One or more of the following had to be present:<br>1. Positive culture and/or microscopy result for <i>Aspergillus</i> from sputum, BAL, bronchial brush or aspirate<br>2. Galactomannan antigen detected in plasma, serum, BALF with any 1 of the following:<br>1) Single serum or plasma: $\geq 1.0$<br>2) BALF fluid: $\geq 1.0$<br>3) Single serum or plasma: $\geq 0.7$ and BAL fluid $\geq 0.8$ | One or more of the following had to be present:<br>1. cytology, direct microscopy, and/or culture indicating presence of <i>Aspergillus</i> spp. in a lower respiratory specimen<br>2. Galactomannan antigen index $>0.5$ in plasma/serum and/or galactomannan antigen $>0.8$ in BALF | One or more of the following had to be present:<br>1. Histopathology or direct microscopic evidence of dichotomous septate hyphae with positive culture for <i>Aspergillus</i> from tissue.<br>2. A positive <i>Aspergillus</i> culture from a bronchoalveolar lavage (BAL).<br>3. A galactomannan                                                                                                              |

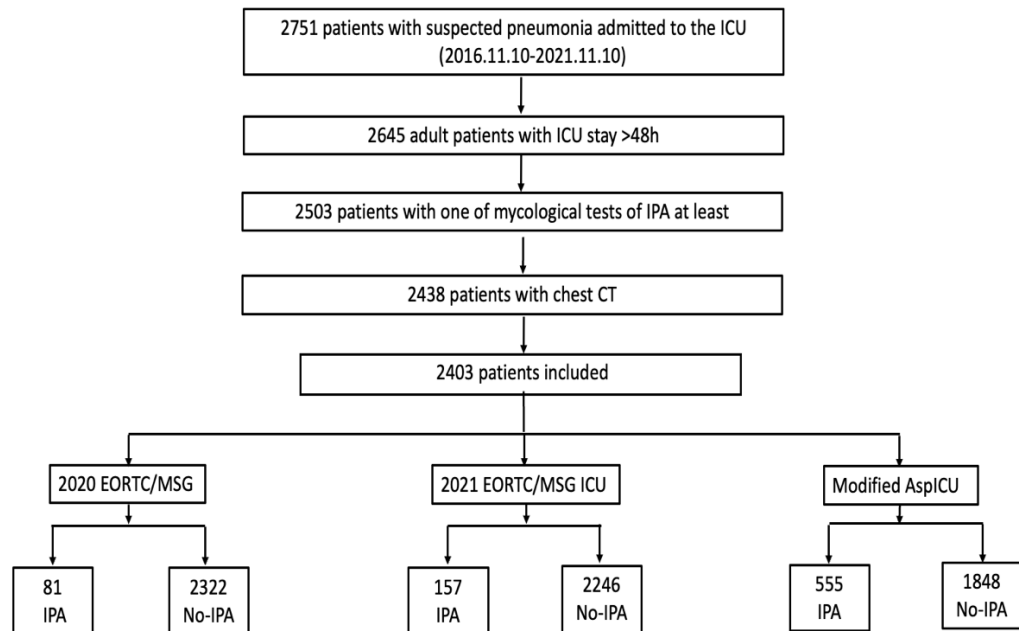
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optical index on BAL  
of  $\geq 1$ .

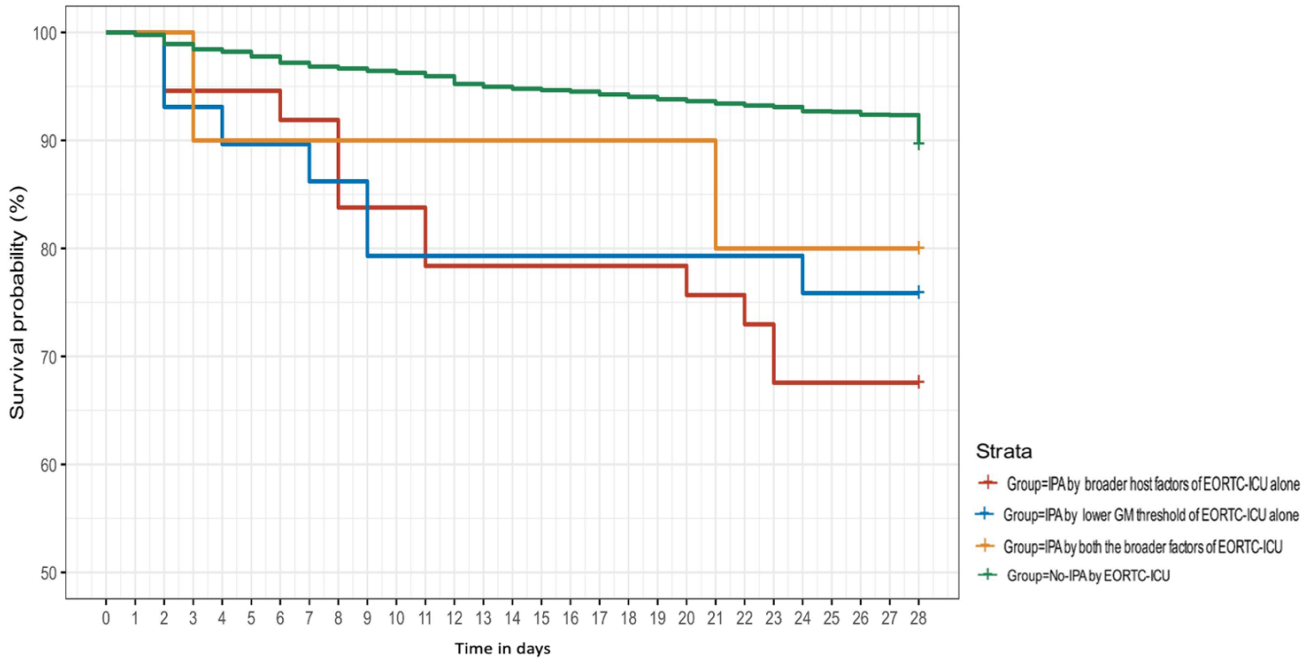
4.A galactomannan  
optical index on serum  
of  $\geq 0 \cdot 5$

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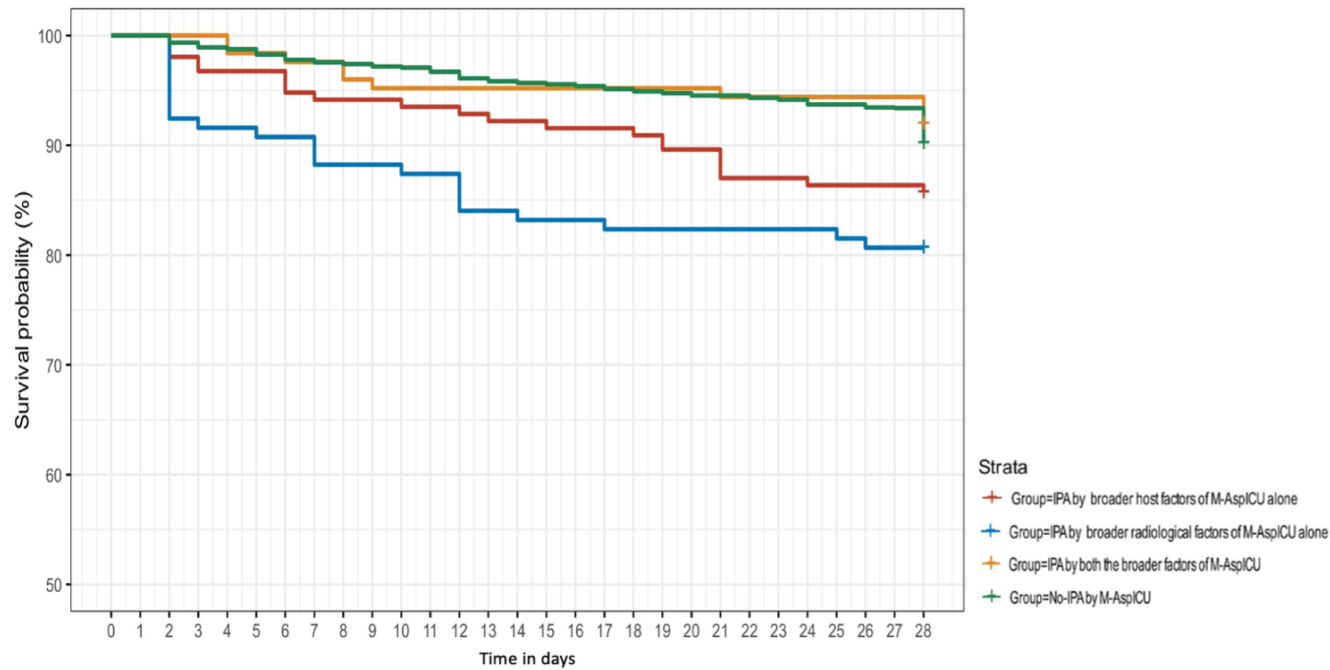
## Supplementary Material 2: Overview of inclusion process for cases, and the corresponding IPA cases according to different criteria



**Supplementary Material 3: Kaplan-Meier for 28-day survival for patients.**



(A)



(B)

**(A)** Kaplan-Meier for 28-day survival for patients with IPA diagnosed by 2021 EORTC/MSG ICU (EORTC-ICU) but missed by 2020 EORTC/MSG

criteria were due to broader host factors alone(n=37), were due to lower GM threshold alone (n=29), were attributed to both (n=10), and patients without IPA (No-IPA) based on the EORTC-ICU criteria(n=2246). For the post hoc pairwise comparison for IPA due to broader host factors alone and No-IPA,  $P<0.001$ , comparison for IPA due to lower GM threshold alone and No-IPA,  $P<0.001$ , as well as IPA were attributed to both and No-IPA,  $P<0.001$ . **(B)** Kaplan-Meier for 28-day survival for patients with IPA diagnosed by M-AspICU but missed by 2021 EORTC/MSG ICU criteria were due to broader host factors alone(n=154), were due to broader radiological factors alone (n=119), were attributed to both (n=125), and patients without IPA (No-IPA) based on the M-AspICU criteria(n=1848). For the post hoc pairwise comparison for IPA due to broader host factors alone and No-IPA,  $P=0.002$ , comparison for IPA due to broader radiological factors alone and No-IPA,  $P=0.001$ , as well as IPA attributed to both and No-IPA,  $P=0.729$ .

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