DIAGNOSTIC CRITERIA FOR IPA

Dr Jaya bharathi Palanivel

Timeline:

Pre-2000: No standardized definition, mainly based on clinical suspicion + culture/histopatholo gy.

2002 – EORTC/MSG Criteria

1st major consensus definition - "proven," "probable," and "possible" IA categories based on host factors, clinical criteria, and microbiological evidence

2008 – Revised EORTC/MSG Criteria

Updated radiological features (halo sign, air crescent sign).

Improved diagnostic microbiology (galactomannan)

2007 – Bulpa Criteria for COPD Patients

Identified COPD patients on steroids as a new risk group

Timeline:

2012 AspICU Criteria (Blot et al.)

For non-neutropenic ICU patients.

Recognized that IA without traditional

Defined 'Putative IPA' based on Clinical +Microbiological + radiological findings

2018 – Modified AspICU Criteria

Adjusted Galactomannan cutoffs for better ICU detection

2020 – CAPA (COVID-19-Associated IPA) Definition

Introduced due to increased IA cases in severe COVID-19 ICU patients

2024- FUNDICU

Extended ICU host factors- COPD, Chronic liver failure, Viral pneumonia

Updated cut off BAL and serum galactomannan testing for ICU patients

Defining Opportunistic Invasive Fungal Infections in Immunocompromised Patients with Cancer and Hematopoietic Stem Cell Transplants: An International Consensus

EORTC/MSG Criteria 2002

- Needs host factor
- Relevant for classic risk factors
- Very limited applicability in the ICU setting.

EORTC/MSG 2002 Original Definitions		
Invasive Fungal Infections; defined by (at least)		
Possible One **host** criterion **AND** One major (or two minor) **clinical** criteria **OR** One **microbiological** criterion	**Probable** One **host** criterion **AND** One major (or two minor) **clinical** criteria **AND** One **microbiological** criterion	**Proven** Histo-/cytopathologic/ microscopic evidence or positive culture from a normally sterile site (PB, CSF, Biopsy)
Host Factors 1 Recent history of neutropenia <0.5x10e9/l for >10 days 2 Prolonged use of corticosteroids >0.3mg/kg/day prednisone equivalent for >3 weeks 3 Persistent fever for >96 h refractory to appropriate broad-spectrum antibacterial treatment in high-risk patients 4 Body temperature either >38 C or <36 C and any of the following predisposing conditions: pro- longed neutropenia (>10 days) in previous 60 days, recent or current use of significant immuno- suppressive agents in previous 30 days, proven or probable invasive fungal infection during previous episode of neutropenia, or coexistence of symptomatic AIDS 5 Signs and symptoms indicating graft-versus-host disease, particularly severe (grade ≥2) or chronic extensive disease		**Fungemia** **Moulds/Yeasts** Blood culture that yields a mould/yeast in the context of a compatible infectious disease process
Clinical Criteria Consistent with microbiological findings, temporally related to current episodic and other potential causes eliminated 1 Lower respiratory tract infection: Major: specific "imaging CT-signs" Minor: lower respiratory tract infection symptoms, pleural rub, new infiltrate not fulfilling major criterion, pleural effusion 2 Sinonasal infection Major: imaging showing sinusitis Minor: upper respiratory tract infection symptoms, nasal ulcer or eschar, periorbital swelling, maxillary tenderness, necrotic lesions/perforation of hard palate 3 CNS infection: Major: imaging showing CNS infection Minor: Focal neurological symptoms and signs, mental changes, meningeal irritation, abnormalities in CSF biochemistry and cell count 4 Disseminated fungal infection: Papular or nodular skin lesions without any other explanation; intraocular findings suggestive of hematogenous fungal chorioretinitis or endophthalmitis 5 Chronic disseminated candidiasis: small, peripheral, target like abscesses in liver and/or spleen demonstrated by imaging		**Deep tissue disease** **Moulds/Yeasts** Histopathologic, cytopathologic (or for moulds: direct microscopic) examination of a needle aspiration or biopsy specimen (for yeasts: excluding mucous membranes) *OR* Recovery of a mould/yeast by culture from a sample obtained by a sterile procedure from a normally sterile and clinical or radiological abnormal site consistent with an infectious disease process (for moulds: excluding BAL, cranial sinus cavity, and urine)
Microbiological Criteria 1 Cytology, direct microscopy or culture: sputum, BAL and bronchus brush samples, sinus aspirate; skin ulcers, fissures 2 Detection of antigen, cell wall constituents or nucleic acid -Galactomannan antigen EIA (platelia): a single plasma, serum, BAL, pleural fluid, urine, CSF sample positive for galactomannan -Glucan assay: a single serum sample positive for beta-D-glucan		**Disseminated and/or pulmonary disease** Must be proven by recovery in culture from a specimen obtained from the affected site, in host with a temporally related illness or consistent with a fungal infectious disease process;

Clin Infect Dis. 2002;34(1):7-14.

Invasive Aspergillosis in Critically Ill Patients without Malignancy

Wouter Meersseman, Stefaan J. Vandecasteele, Alexander Wilmer, Eric Verbeken, Willy E. Peetermans, and Eric Van Wijngaerden

Medical Intensive Care Unit and Infectious Diseases Unit, Department of General Internal Medicine; and Department of Pathology, University Hospital, Leuven, Belgium

TABLE 1. CHARACTERISTICS OF ALL OBSERVED CASES

	All (*n* = 127)	Proven IA (*n* = 56)	Probable IA (*n* = 49)	Possible IA (*n* = 2)	Colonization (*n* = 20)
Age, yr, mean	61	59	63	61	64
Sex, male, n	84	39	35	2	8
Patients with hematologic malignancy, n	38	26	12	0	0
Patients without hematologic malignancy, n	89	30	37	2	20
COPD, n	35	12	21	2	0
Solid organ transplants, n	9	4	5	0	0
Systemic disease, n	17	6	8	0	3
Cirrhosis, n	6	3	0	0	3
Other, n	22	5	3	0	14
SAPS II, mean	54	57	52	43	54
Predicted mortality, %	53	58	49	31	51
Observed mortality, %	86	98	90	0	50
ICU length of stay, d	20	14	23	32	28
Hemodialysis in ICU, n	54	27	20	0	7
Mechanical ventilation, n	123	56	47	2	18
Neutropenia, n	19	12	6	0	1
Autopsy, n	76	52	19	0	5

- Proven IA - observed 98% mortality , followed by probable IA- 90% mortality.
- IA without hematologic malignancy ,n=89
- COPD- mc underlying condition in non hematological patients (n=33)o
- The majority of IA patients required mechanical ventilation (123 out of 127).

Retrospective study between 2000 and 2003 ,
127 patients out of 1,850 admissions (6.9%) hospitalized had microbiological or histopathologic evidence of Aspergillus during their ICU stay

Criteria- EORTC/MSG 2002

TABLE 2. CLINICAL CHARACTERISTICS OF PATIENTS WITHOUT HEMATOLOGICAL MALIGNANCY WITH PROVEN OR PROBABLE IA

	All (*n* = 67)	COPD (*n* = 33)	Systemic Disease (*n* = 14)	Liver Cirrhosis (*n* = 3)	Solid Organ Transplants (*n* = 9)	Other (*n* = 8)
Age, yr, mean	65	69	60	55	51	73
SAPS II, mean	52	49	50	64	47	66
Predicted mortality, %	48	43	44	71	40	73
Observed mortality, %	91	85	93	100	100	100
Length of stay, d	21	23	18	13	22	14
Culture positive*	56/67	31/33	10/14	1/3	6/9	8/8
Asp Ag** Positive*	27/51	12/25	7/11	0/0	4/9	4/6
Autopsy positive*	27/41	12/19	6/9	3/3	3/6	3/4

*Tested positive/tested.
**Serum aspergillus antigen (galactomannan assay by means of ELISA).

American Journal of Respiratory and Critical Care Medicine. 2004;170:622-628.

Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease

P. Bulpa*, A. Dive* and Y. Sibille#

TABLE 1 Definitions of invasive pulmonary aspergillosis (IPA) in chronic obstructive pulmonary disease (COPD) patients

Proven IPA	Histopathological or cytopathological examination, from needle aspiration or biopsy specimen obtained from any pulmonary lesion present for <3 months, showing hyphae consistent with Aspergillus and evidence of associated tissue damage, if accompanied by any one of the following: 1) Positive culture of Aspergillus spp. from any LRT sample. 2) Positive serum antibody/antigen test for *A. fumigatus* (including precipitins). 3) Confirmation that the hyphae observed are those of Aspergillus by a direct molecular, immunological method and/or culture.
Probable IPA	As for proven IPA but without confirmation that Aspergillus is responsible (points 1, 2 and 3 are not present or tested). OR COPD patient, usually treated with steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea#, suggestive chest imaging¶ (radiograph or CT scan; <3 months+) and one of the following: 1) Positive culture§ and/or microscopy for Aspergillus from LRT. 2) Positive serum antibody test for *A. fumigatus* (including precipitins). 3) Two consecutive positive serum galactomannan tests.
Possible IPA	COPD patient, usually treated by steroids and severe according to GOLD (stage III or IV), with recent exacerbation of dyspnoea#, suggestive chest imaging¶ (radiograph or CT scan; <3 months+), but without positive Aspergillus culture or microscopy from LRT or serology.
Colonisation	COPD patient with positive Aspergillus culture from LRT *without* exacerbation of dyspnoea, bronchospasm or new pulmonary infiltrate.

ASP ICU Project

A Clinical Algorithm to Diagnose Invasive Pulmonary Aspergillosis in Critically Ill Patients

Stijn I. Blot[1], Fabio Silvio Taccone[2], Anne-Marie Van den Abeele[3], Pierre Bulpa[4], Wouter Meersseman[5], Nele Brusselaers[1], George Dimopoulos[6], José A. Paiva[7], Benoit Misset[8], Jordi Rello[9], Koenraad Vandewoude[1], Dirk Vogelaers[1], and the *Asp*ICU Study Investigators*

- Study Design: Multicenter observational study (n=524) conducted between nov 2006-jan 2011, with histopathology (n=115) as the gold standard
- Algorithm Criteria:
- a)Aspergillus-positive Respiratory Sample

b) Clinical Signs/Symptoms

c) Abnormal Imaging (e.g., X-ray, CT findings)

d) Host Risk Factors/Mycological

- Putative IPA: All 4 criteria met
- Colonization: Any 1 criterion absent

Am J Respir Crit Care Med. 2012;186(1):56-64

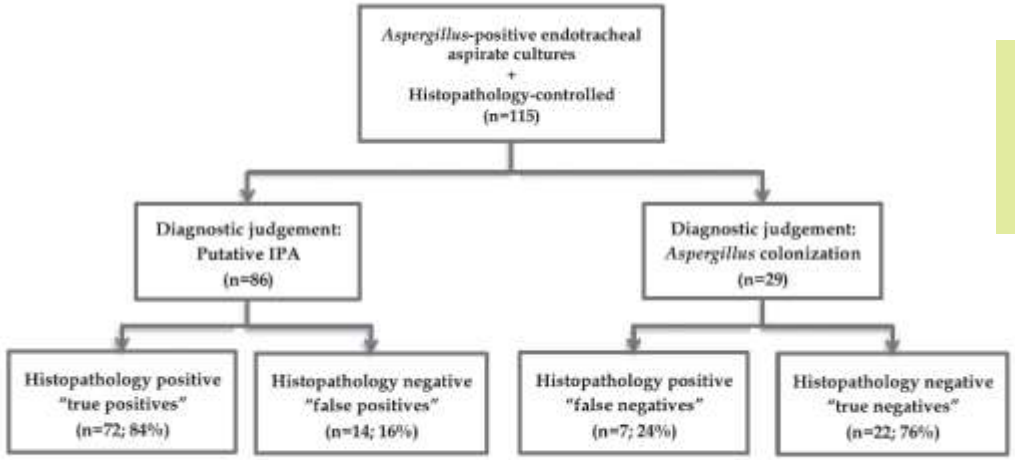
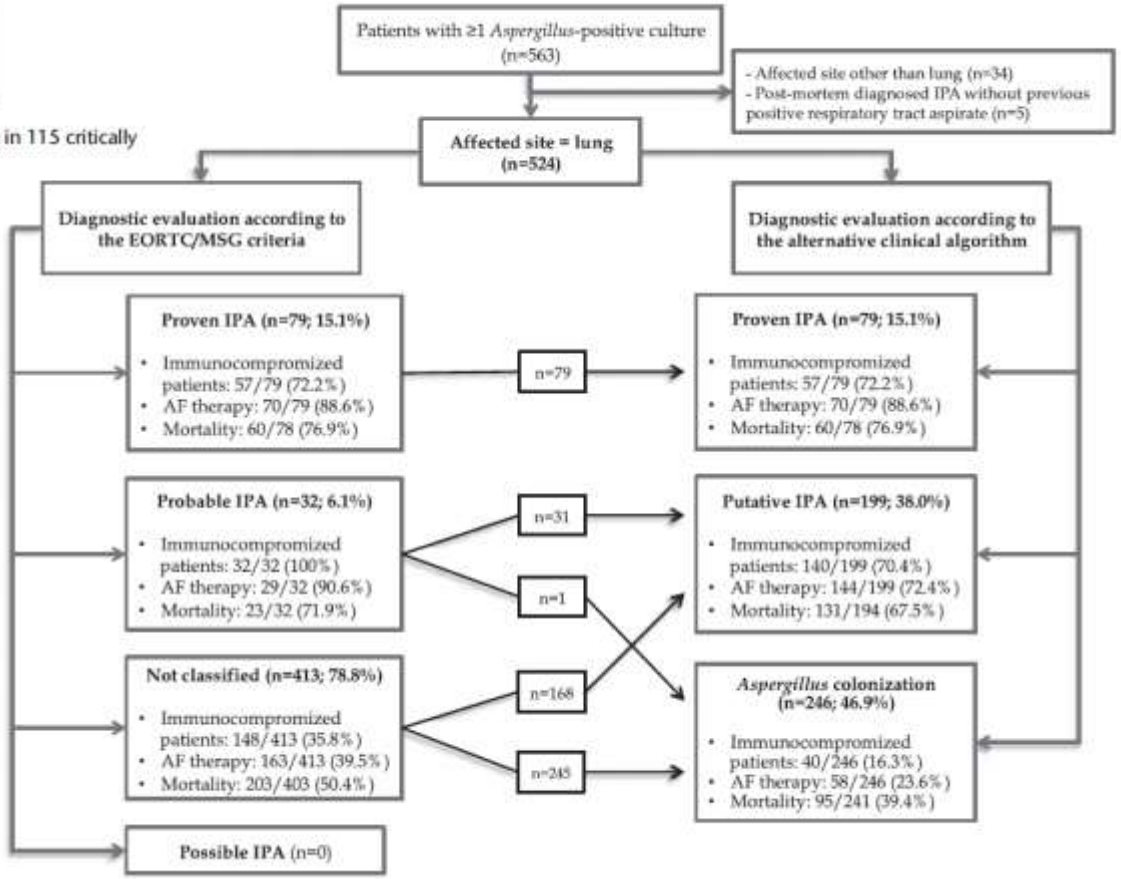


Figure 1. Predictive value of the clinical algorithm to discriminate invasive pulmonary aspergillosis (IPA) from *Aspergillus* colonization in 115 critically ill patients with *Aspergillus*-positive endotracheal aspirates and histopathologic examination.

Among 115 patients, the algorithm had a sensitivity of 92% (95% CI, 83-96%) and a specificity of 61% (95% CI, 45-75%)

According to EORTC /MSG criteria:
Probable 32 and 413 – not classified

According to Asp ICU , Putative 199 and colonization 246



Am J Respir Crit Care Med. 2012;186(1):56-64

Entry criteria - needed

Radiology – any non specific infiltrates included

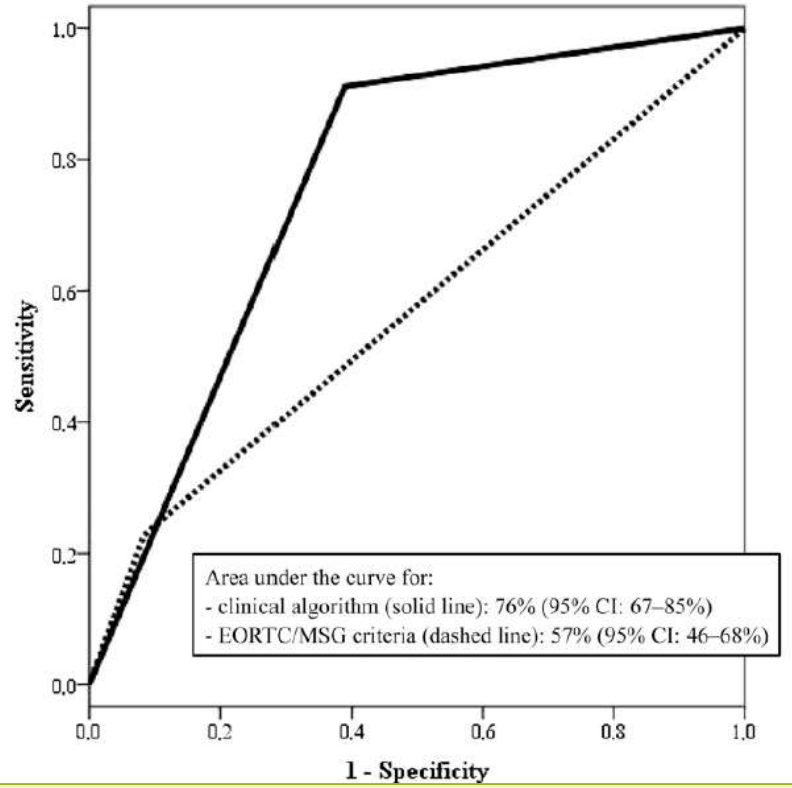
TABLE 3. DIAGNOSTIC CRITERIA FOR INVASIVE PULMONARY ASPERGILLOSIS IN INTENSIVE CARE UNIT PATIENTS, CLASSIFIED ACCORDING TO THE RESULTS OF HISTOPATHOLOGY EXAMINATION AND CLINICAL ALGORITHM

	Pathology Positive (Proven IPA)		Pathology Negative (Proven Colonization)		Operating Characteristics for Distinct Criteria within the Algorithm			
	TP ($n = 72$)	FN ($n = 7$)	FP ($n = 14$)	TN ($n = 22$)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
ia of the clinical algorithm for diagnosing probable IPA								
spergillus-positive endotracheal aspirate	72 (100)	7 (100)	14 (100)	22 (100)				
2. Compatible signs	72 (100)	7 (100)	14 (100)	13 (59.1)	100	25	47	100
Fever refractory to at least 3 d of appropriate antibiotic therapy	40 (55.6)	6 (85.7)	4 (28.6)	3 (13.6)				
Recrudescent fever after ⩾48 h of defervescence while still on antibiotics and without other apparent cause	2 (2.8)	0	1 (7.1)	2 (9.1)				
Pleuritic chest pain	5 (6.9)	0	0	0				
Pleuritic rub	3 (4.2)	0	0	0				
Dyspnea	37 (51.4)	3 (42.9)	6 (42.9)	7 (31.8)				
Hemoptysis	13 (18.1)	0	3 (21.4)	0				
Worsening respiratory insufficiency despite appropriate antibiotic therapy and ventilatory support	51 (70.8)	4 (57.1)	8 (57.1)	4 (18.2)				
3. Abnormal thoracic medical imaging on CT scan or X-ray	72 (100)	7 (100)	14 (100)	20 (90.9)	100	6	41	100
Diffuse reticular or alveolar opacities	17 (23.6)	3 (42.9)	8 (57.1)	5 (22.7)				
Nonspecific infiltrates and consolidation	49 (68.1)	4 (57.1)	5 (35.7)	15 (68.2)				
Pleural fluid	28 (38.9)	3 (42.9)	6 (42.9)	5 (22.7)				
Wedge-shaped infiltrate	8 (11.1)	3 (42.9)	0	0				
Well-shaped nodule(s)	19 (26.4)	2 (28.6)	3 (21.4)	4 (18.2)				
Air-crescent sign	1 (1.4)	0	1 (7.1)	0				
Halo sign	5 (6.9)	0	0	1 (4.5)				
Cavitation	7 (9.7)	0	0	1 (4.5)				
4a. Host risk factors	67 (93.1)	0	14 (100)	5 (22.7)	84	47	51	81
Neutropenia (<500 neutrophils/mm^3)	6 (8.3)	0	2 (14.3)	0				
Malignancy treated with cytotoxic agents	16 (22.2)	0	4 (28.6)	0				
Glucocorticoid treatment	52 (72.2)	0	12 (85.7)	5 (22.7)				
Inherited severe immunodeficiency	3 (4.2)	0	0	0				
4b. Semiquantitative *Aspergillus*-positive culture of BAL fluid + positive direct microscopy	31 of 51 (60.8)	0 of 3 (0)	1 of 11 (9.1)	0 of 5 (0)	94	57	87	77
Criteria for proven IPA present								
Biopsy positive	34 of 34 (100)	3 of 3 (100)	0 of 9 (0)	0 of 15 (0)				
Autopsy positive	38 of 38 (100)	4 of 4 (100)	0 of 5 (0)	0 of 7 (0)				

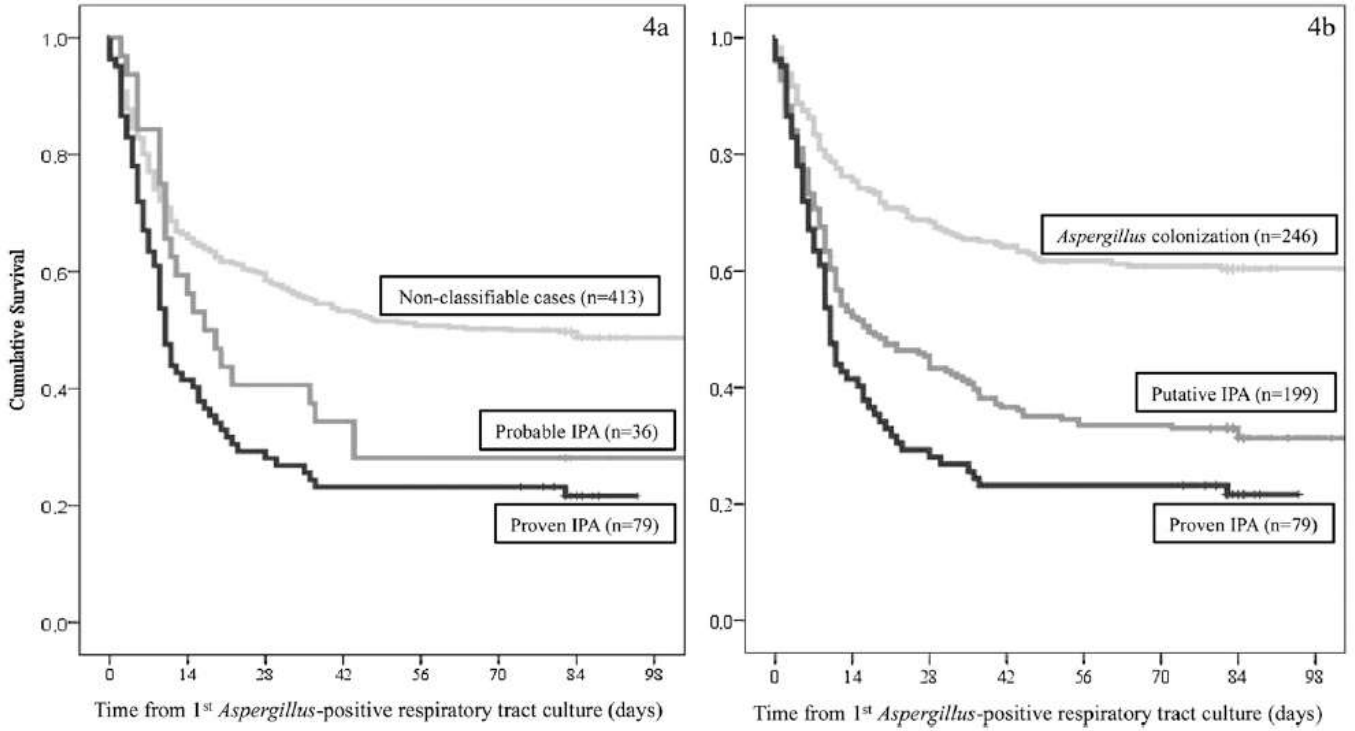
Definition of abbreviations: BAL = bronchoalveolar lavage; FN = false negatives; FP = false positives; IPA = invasive pulmonary aspergillosis; NPV = negative predictive value; PPN = positive predictive value; Sens = sensitivity; Spec = specificity; TP = true positives.

Am J Respir Crit Care Med. 2012;186(1):56-64

ROC analyses for diagnosing invasive pulmonary aspergillosis by clinical algorithm and EORTC /MSG



Survival curves a) EORTC b) Clinical algorithm
Log rank for survival distributors in a and b , P< 0.001



Non-classified cases had higher mortality than Aspergillus colonization (39.5% vs. 23.6%; P < 0.001)

Am J Respir Crit Care Med. 2012;186(1):56-64

ASP ICU Project

1. The clinical algorithm effectively distinguishes Aspergillus respiratory tract colonization from invasive pulmonary aspergillosis (IPA) in critically ill patients, thus aiding clinical decision-making.

2. The algorithm requires an Aspergillus-positive culture, potentially excluding some IPA cases with negative cultures, limiting its applicability.

3. The study's selection is of only histopathology-controlled cases , biopsies are not possible in most of Critical ill cases

Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study

Alexander F A D Schauwvlieghe, Bart J A Rijnders*, Nele Philips, Rosanne Verwijs, Lore Vanderbeke, Carla Van Tienen, Katrien Lagrou, Paul E Verweij, Frank L Van de Veerdonk, Diederik Gommers, Peter Spronk, Dennis C J J Bergmans, Astrid Hoedemaekers, Eleni-Rosalina Andrinopoulou, Charlotte H S B van den Berg, Nicole P Juffermans, Casper J Hodiamont, Alieke G Vonk, Pieter Depuydt, Jerina Boelens, Joost Wauters, on behalf of the Dutch-Belgian Mycosis study group*

Modified Asp ICU criteria - 2018

Host factors- not needed

Clinical criteria - same

Panel: The modified definition of invasive pulmonary aspergillosis

The definition of invasive pulmonary aspergillosis was modified from the *AspICU* algorithm and was based on the presence of clinical, radiological, and mycological criteria in all invasive pulmonary aspergillosis cases.

This modified invasive pulmonary aspergillosis definition did not require a European Organisation for Research and Treatment of Cancer (EORTC)-defined host factor because otherwise patients with influenza but without an EORTC host factor could never fulfil the definition, as long as influenza is not part of the EORTC host factor definition.

Clinical criteria

One of the following signs or symptoms had to be present:

- Fever refractory to at least 3 days of appropriate antibiotic therapy.
- Recrudescent fever after a period of defeverescence of at least 48 h while still on antibiotics and without other apparent cause.
- Dyspnoea.
- Haemoptysis.
- Pleural friction rub or chest pain.
- Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support.

Radiological criteria

Any infiltrate on pulmonary imaging by portable chest x-ray or CT scan of the lungs. This radiological definition was different from the EORTC-defined radiological criteria (eg, halo sign or air-crescent sign) because these EORTC criteria apply to patients with prolonged neutropenia but are of little use for ICU patients.

Mycological criteria

One or more of the following had to be present:

- Histopathology or direct microscopic evidence of dichotomous septate hyphae with positive culture for *Aspergillus* from tissue.
- A positive *Aspergillus* culture from a bronchoalveolar lavage (BAL).
- A galactomannan optical index on BAL of ≥1.
- A galactomannan optical index on serum of ≥0·5.

The Platelia Aspergillus test was used for galactomannan detection in all centres (Bio-Rad Laboratories, Marnes-la-Coquette, France). *Aspergillus* species were identified by their culture characteristics and microscopic morphology.

- Typical radiological findings not necessary
- Any infiltrate on pulmonary imaging

Mycology:
Biopsy proven / culture
GMI - ≥ 0.5 serum, ≥ 1 Bal

Lancet Respir Med. 2018;6(10):782-92.

BASELINE CHARACTERISTICS

	Influenza cohort (n=432)	With invasive pulmonary aspergillosis (n=83)	Without invasive pulmonary aspergillosis (n=349)	p value
Baseline characteristics				
Mean age, years (SD)	59 (15)	60 (12)	59 (16)	0·35
Male sex	240 (56%)	56 (67%)	184 (53%)	0·015
Mean APACHE II score on admission (SD)	22 (8)	25 (9)	22 (7)	0·005
Body-mass index >30 kg/m²	93/410 (23%)	17/83 (20%)	76/327 (23%)	0·59
Diabetes	88 (20%)	10 (12%)	78 (22%)	0·036
Liver cirrhosis	25 (6%)	5 (6%)	20 (6%)	1·0
Chronic kidney disease*	71 (16%)	16 (19%)	55 (16%)	0·44
Known risk factors				
EORTC/MSG host factor	117 (27%)	38 (46%)	79 (23%)	<0·0001
Haematological malignancy	66 (15%)	22 (27%)	44 (13%)	0·002
Solid organ transplant	32 (7%)	11 (13%)	21 (6%)	0·024
Solid organ malignancy	21 (5%)	4 (5%)	17 (5%)	1·0
Neutropenia	22 (5%)	11 (13%)	11 (3%)	0·001
Chronic obstructive pulmonary disease	79 (18%)	13 (16%)	66 (19%)	0·49
Studied risk factors				
Corticosteroids 28 days before ICU	145/426 (34%)	46/82 (56%)	99/344 (29%)	<0·0001
Median dose corticosteroids 28 days before ICU admission (IQR), mg/kg/day	0·14 (0·06–0·28)	0·22 (0·10–0·33)	0·10 (0·06–0·24)	0·003
Smoking in the past year	114/332 (34%)	26/61 (43%)	88/271 (32%)	0·13
ICU data				
Mechanical ventilation	326 (75%)	75 (90%)	251 (72%)	0·0004
Mechanical ventilation days (IQR)	11 (5–21)	14 (9–31)	9 (4–17)	0·001
Nitric oxide or high-frequency oscillation ventilation	42 (10%)	13 (16%)	29 (8%)	0·04
Extracorporeal membrane oxygenation	52 (12%)	16 (19%)	36 (10%)	0·024
Vasopressors	287/423 (67%)	67/82 (81%)	220/341 (65%)	0·002
Renal replacement therapy	100/423 (24%)	35/83 (42%)	65/340 (19%)	<0·0001
Outcome data				
Median days of ICU stay (IQR)	11 (6–23)	19 (12–38)	9 (5–20)	<0·0001
ICU mortality	107 (25%)	37 (45%)	70 (20%)	<0·0001
Hospital mortality	133 (31%)	41 (49%)	92 (26%)	<0·0001
90-days mortality after ICU admission	141 (33%)	42 (51%)	99 (28%)	0·0001

	All EORTC/MSG negative (non-immunocompromised) patients (n=630)	Influenza case group (n=315)*	Control group (n=315)*	p value
Baseline characteristics				
Mean age, years (SD)	59 (17)	58 (16)	60 (17)	0·15
Male sex	371 (59%)	169 (54%)	202 (64%)	0·008
Mean APACHE II score on admission (SD)	23 (8)	22 (8)	23 (8)	0·29
Median body-mass index, kg/m² (IQR), missing	25 (22–29), 21	27 (23–30), 18	24 (22–28), 3	<0·0001
Diabetes	114 (19%)	63 (20%)	51 (16%)	0·21
Liver cirrhosis	44 (7%)	18 (6%)	26 (8%)	0·21
Chronic kidney disease†	69 (11%)	31 (10%)	38 (12%)	0·37
Chronic obstructive pulmonary disease	123 (20%)	68 (22%)	55 (17%)	0·19
Corticosteroids				
Corticosteroids 28 days before ICU	99/619 (16%)	57/304 (19%)	42/315 (13%)	0·005
Median dose corticosteroids 28 days before ICU admission (IQR), mg/kg/day, missing	0·078 (0·054–0·176), 22	0·070 (0·054–0·171), 10	0·080 (0·053–0·179), 12	0·79
ICU data				
Mechanical ventilation	475 (75%)	246 (78%)	229 (73%)	0·12
Median ventilation days (IQR), missing	9 (4–18), 35	11 (5–21), 26	4 (4–14), 9	0·002
Nitric oxide or high-frequency oscillation ventilation	64 (10%)	37 (12%)	27 (9%)	0·17
Extracorporeal membrane oxygenation	65 (10%)	45 (14%)	20 (6%)	0·04
Median extracorporeal membrane oxygenation days (IQR)	10 (6–20)	11 (8–21)	9 (5–18)	0·44
Vasopressors	415 (66%)	216 (69%)	199 (63%)	0·17
Renal replacement therapy	103 (16%)	61/307 (20%)	42 (13%)	0·03
Outcome data				
ICU mortality	125 (20%)	58 (18%)	67 (21%)	0·37
Hospital mortality	164 (26%)	76 (24%)	88 (28%)	0·28
90-day mortality after ICU admission	177 (28%)	78 (25%)	99 (31%)	0·70
Median days of ICU stay (IQR), missing	11 (6–21), 19	11 (6–23), 15	10 (6–18), 4	0·15
Invasive pulmonary aspergillosis	61 (10%)	45 (14%)	16 (5%)	<0·0001

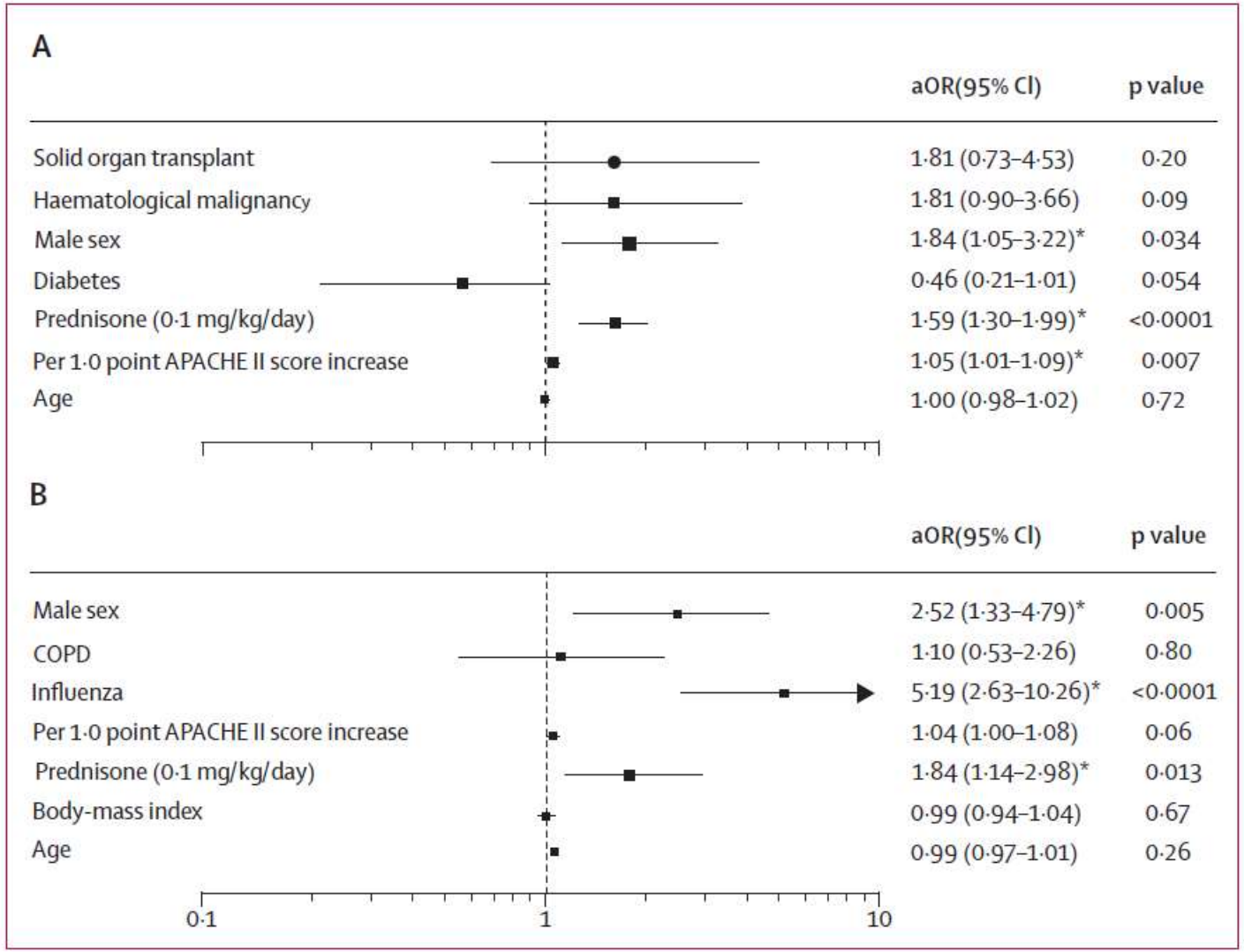
Lancet Respir Med. 2018;6(10):782-92.

	Number of patients in the influenza cohort with invasive pulmonary aspergillosis (n=83)
BAL culture positive	50/80 (63%)*
BAL galactomannan test positive	67/76 (88%)
Serum galactomannan test positive	20/31 (65%)
EORTC/MSG criteria	
Proven	16 (19%)
Probable	20 (24%)
Not classifiable	47 (57%)
AspICU criteria	
Proven	16 (19%)
Putative	32 (39%)
Coloniser	5 (6%)
Not classifiable	30 (36%)
Initial treatment	
Voriconazole	61 (73%)
Echinocandins	2 (2%)
Combination (triazole plus echinocandins)	9 (11%)
Liposomal amfotericin B	4 (5%)
No treatment	7 (8%)

Data are n (%) or n/N (%). BAL=bronchoalveolar lavage. EORTC/MSG=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. *Procedure was not adequate in one sample.

Table 2: **Invasive pulmonary aspergillosis characteristics of patients in the influenza cohort**

Forest plots of risk factors for the development of invasive pulmonary aspergillosis



Lancet Respir Med. 2018;6(10):782-92.

- This study is the largest on invasive pulmonary aspergillosis in ICU influenza patients, showing influenza infection as an independent risk facto
- Influenza increases the risk of invasive pulmonary aspergillosis (IPA) in ICU patients from 5% to 14%, with high mortality rates (45% overall, 33% in previously healthy individuals).
- Diagnosis is complicated by nonspecific radiology and the absence of classic host factors.
- A modified definition with stringent mycological criteria was used.
- Need for antifungal prophylaxis are to be studied in high-risk groups.
- Retrospective design, and a lack of a standardized diagnostic approach for invasive pulmonary aspergillosis.

Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion

IAPA- 2020

Table 1 Proposed case definition for IAPA in ICU patients

Entry criteria: influenza-like illness + positive influenza PCR or antigen + temporally relationship		
	***Aspergillus* tracheobronchitis**	**IAPA in patients without documented *Aspergillus* tracheobronchitis**
Proven	Biopsy or brush specimen of airway plaque, pseudomembrane or ulcer showing hyphal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue	Lung biopsy showing invasive fungal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue
Probable	Airway plaque, pseudomembrane or ulcer and at least one of the following: Serum GM index > 0.5 *or* BAL GM index ≥ 1.0 *or* Positive BAL culture *or* Positive tracheal aspirate culture *or* Positive sputum culture *or* Hyphae consistent with *Aspergillus*	**A**: Pulmonary infiltrate and at least one of the following: Serum GM index > 0.5 *or* BAL GM index ≥ 1.0 *or* Positive BAL culture ***OR*** **B**: Cavitating infiltrate (not attributed to another cause) and at least one of the following: Positive sputum culture *or* Positive tracheal aspirate culture

Intensive Care Med. 2020;46(11):2032-2035

Table 1 Proposed case definition for IAPA in ICU patients

Entry criteria: influenza-like illness + positive influenza PCR or antigen + temporally relationship		
	Aspergillus tracheobronchitis	IAPA in patients without documented *Aspergillus* tracheobronchitis
Proven	Biopsy or brush specimen of airway plaque, pseudomembrane or ulcer showing hyphal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue	Lung biopsy showing invasive fungal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue

Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion

Only 3 category

Proven IAPA
Probable IAPA
No IAPA

Aspergillus tracheobronchitis were observed

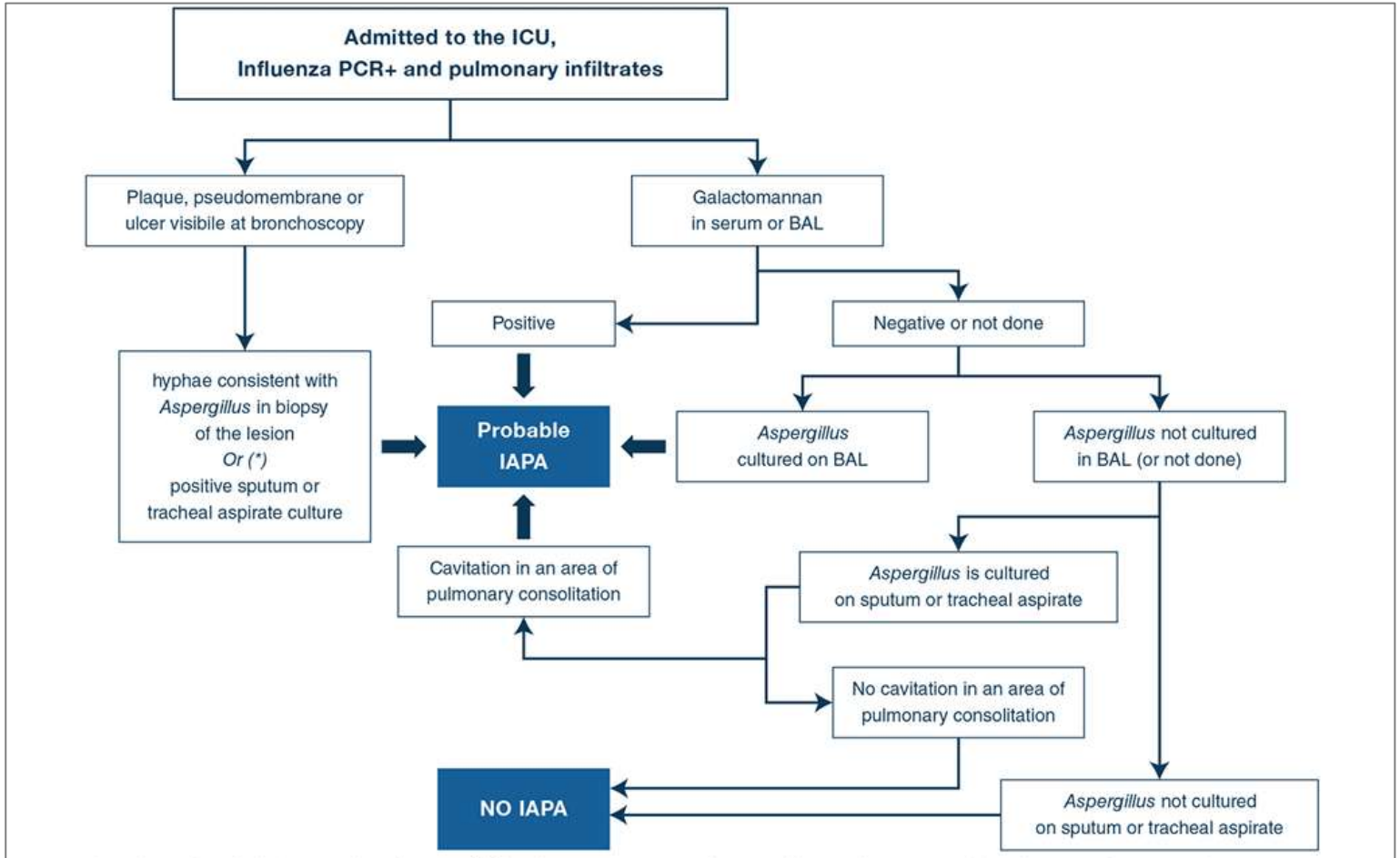


Fig. 1 Flowchart of probable IAPA classification. (*)If hyphae consistent with *Aspergillus* are documented in a biopsy of an airway lesion AND *Aspergillus* is grown from sputum or a tracheal aspirate, the case fulfills the definition of proven IAPA

Intensive Care Med. 2020;46(11):2032-2035

Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance

CAPA- 2020 ISHAM

Proposed case definition for CAPA (adapted from EORTC and MSGERC[3], AspICU[47], and expert case definitions of IAPA[48])

Tracheobronchitis or other pulmonary form (proven)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	..	At least one of the following: histopathological or direct microscopic detection of fungal hyphae, showing invasive growth with associated tissue damage; or aspergillus recovered by culture or microscopy or histology or PCR obtained by a sterile aspiration or biopsy from a pulmonary site, showing an infectious disease process	..
Tracheobronchitis (probable)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Tracheobronchitis, indicated by tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis	At least one of the following: microscopic detection of fungal elements in bronchoalveolar lavage, indicating a mould; positive bronchoalveolar lavage culture or PCR;† serum galactomannan index >0·5 or serum LFA index >0·5;‡ or bronchoalveolar lavage galactomannan index ≥1·0 or bronchoalveolar lavage LFA index ≥1·0‡	..
Other pulmonary forms (probable)	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Pulmonary infiltrate, preferably documented by chest CT, or cavitating infiltrate (not attributed to another cause)	At least one of the following: microscopic detection of fungal elements in bronchoalveolar lavage, indicating a mould; positive bronchoalveolar lavage culture;† serum galactomannan index >0·5 or serum LFA index >0·5;‡ bronchoalveolar lavage galactomannan index ≥1·0 or bronchoalveolar lavage LFA index ≥1·0;‡ two or more positive aspergillus PCR tests in plasma, serum, or whole blood;† a single positive aspergillus PCR in bronchoalveolar lavage fluid (<36 cycles);† or a single positive aspergillus PCR in plasma, serum, or whole blood, and a single positive in bronchoalveolar lavage fluid (any threshold cycle permitted)†	..

The Lancet Infectious Diseases, 21(6), e149–e162

Other pulmonary forms (possible)[12]§	Patient with COVID-19 needing intensive care and a temporal relationship (entry criterion)	Pulmonary infiltrate, preferably documented by chest CT, or cavitating infiltrate (not attributed to another cause)	At least one of the following: microscopic detection of fungal elements in non-bronchoscopic lavage indicating a mould; positive non-bronchoscopic lavage culture;† single non-bronchoscopic lavage galactomannan index >4·5; non-bronchoscopic lavage galactomannan index >1·2 twice or more; or non-bronchoscopic lavage galactomannan index >1·2 plus another non-bronchoscopic lavage mycology test positive (non-bronchoscopic lavage PCR or LFA)	..

Expert case definitions for IAPA[48]

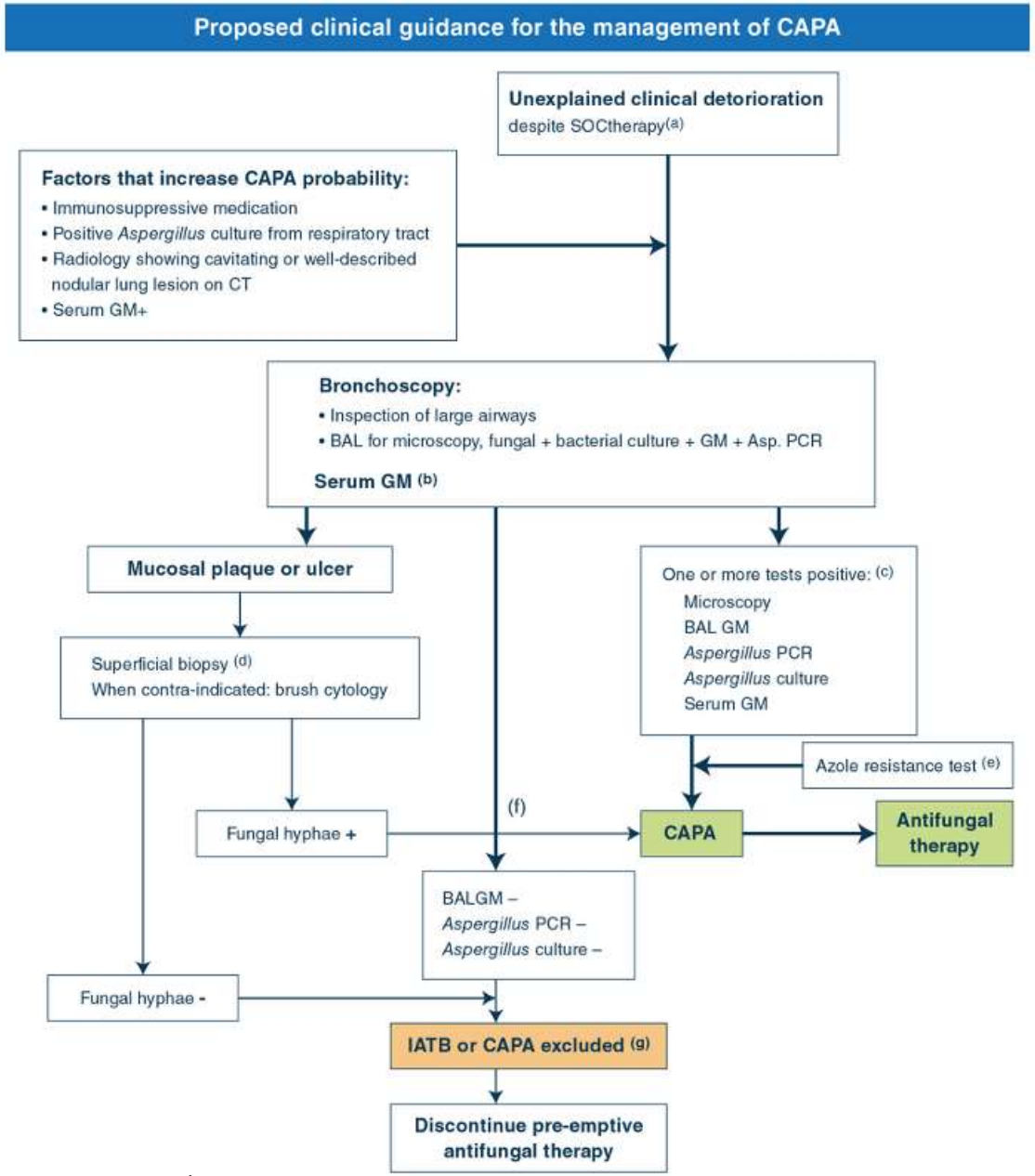
Tracheobronchitis (probable)	Influenza-like illness, positive influenza PCR or antigen, and temporal relationship (entry criterion)	Airway plaque, pseudomembrane, or ulcer	At least one of the following: serum galactomannan index >0·5, bronchoalveolar lavage galactomannan index ≥1·0, positive bronchoalveolar lavage culture, positive non-bronchoscopic lavage culture, positive sputum culture, or hyphae in direct microscopy consistent with *Aspergillus* spp	..
Other pulmonary forms (probable)	Influenza-like illness, positive influenza PCR or antigen, and temporal relationship (entry criterion)	Pulmonary infiltrate (not attributed to another cause)	At least one of the following: serum galactomannan index >0·5, bronchoalveolar lavage galactomannan index ≥1·0, or positive bronchoalveolar lavage culture	..
Other pulmonary forms (probable)	Influenza-like illness, positive influenza PCR or antigen, and temporal relationship (entry criterion)	Cavitating infiltrate (not attributed to another cause)	One of the following: positive sputum culture or positive tracheal aspirate culture	..

The Lancet Infectious Diseases, 21(6), e149–e162

CONFERENCE REPORTS AND EXPERT PANEL

Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis

CAPA- 2021 Task force



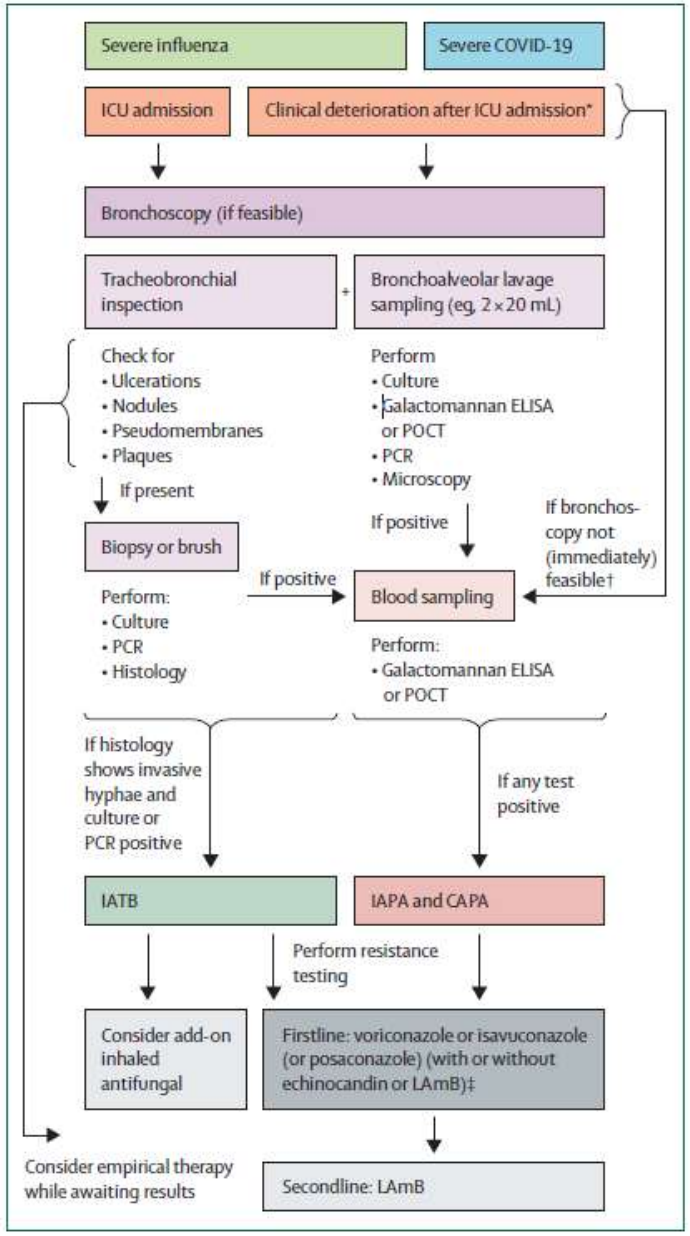
Intensive Care Med. 2021;47(8):1030-1042.

Comparison between characteristics of IAPA and CAPA

Factor	IAPA	CAPA
Host/Risk	57% EORTC/MSGERC host factor negative [9]	85% EORTC/MSGERC host factor negative [59, 60]
	IAPA associated with corticosteroid use [7]	IPA developed in SARS-2003-infected patients receiving corticosteroids [61]
		Lymphopenia and chemokine-producing monocyte-derived FCN1 + macrophages causing hyperinflammation [62]
Virus	Cell entry through sialic acids-2,6Gal: epithelial layer in lung including larger airways [63]	Cell entry through ACE2: type 2 pneumocytes and ciliated cells [64]
	Immune modulation by suppression of the NADPH oxidase complex [65]	No evidence for immunomodulatory effect on known antifungal host defense mechanisms, although this has not been extensively studied yet
Fungal infection	Invasive *Aspergillus* tracheobronchitis in up to 55% of patients [7–9]	Invasive *Aspergillus* tracheobronchitis not yet reported [59, 60]
	Median time between ICU admission and IAPA diagnosis 2–3 days [7–9]	Median time between ICU admission and CAPA diagnosis 6 days [59]
Aspergillus diagnostics	BAL GM positive in > 88% [7–9]	BAL GM commonly positive, diagnostic performance currently unknown [59, 60]
	Serum GM positive in 65% [7–9]	Serum GM positive in 3 of 14 (21%) COVID-19 patients [59, 60]
Secondary infections	In 80 of 342 (23.4%) ICU patients, most frequent pathogens *S. pneumoniae*, *Pseudomonas aeruginosa* and *S. aureus* [66]	In four of 13 (31%) ICU patients, pathogens not specified [67]
ICU mortality	45% in IAPA compared with 20% in influenza without IAPA ($p < 0.0001$) [9]	33% in CAPA cases compared with 17% in COVID-19 without CAPA ($p = 0.4$) [59] (although mortality rates due to COVID-19 without CAPA vary enormous between countries and we have no clear data yet on the true mortality in ICU of COVID-19)

Influenza-associated and COVID-19-associated pulmonary aspergillosis in critically ill patients

Simon Feys, Agostinho Carvalho, Cornelius J Clancy, Jean-Pierre Gangneux, Martin Hoenigl, Katrien Lagrou, Bart J A Rijnders, Laura Seldeslachts, Lore Vanderbeke, Frank L van de Veerdonk, Paul E Verweij, Joost Wauters



Pulmonary Aspergillosis in Patients with Suspected Ventilator-associated Pneumonia in UK ICUs

Laura Loughlin[1], Thomas P. Hellyer[2], P. Lewis White[3], Danny F. McAuley[1], Andrew Conway Morris[4], Raquel B. Posso[3] Malcolm D. Richardson[5], David W. Denning[6], A. John Simpson[2*], and Ronan McMullan[1*]

Modified asp ICU- 2020

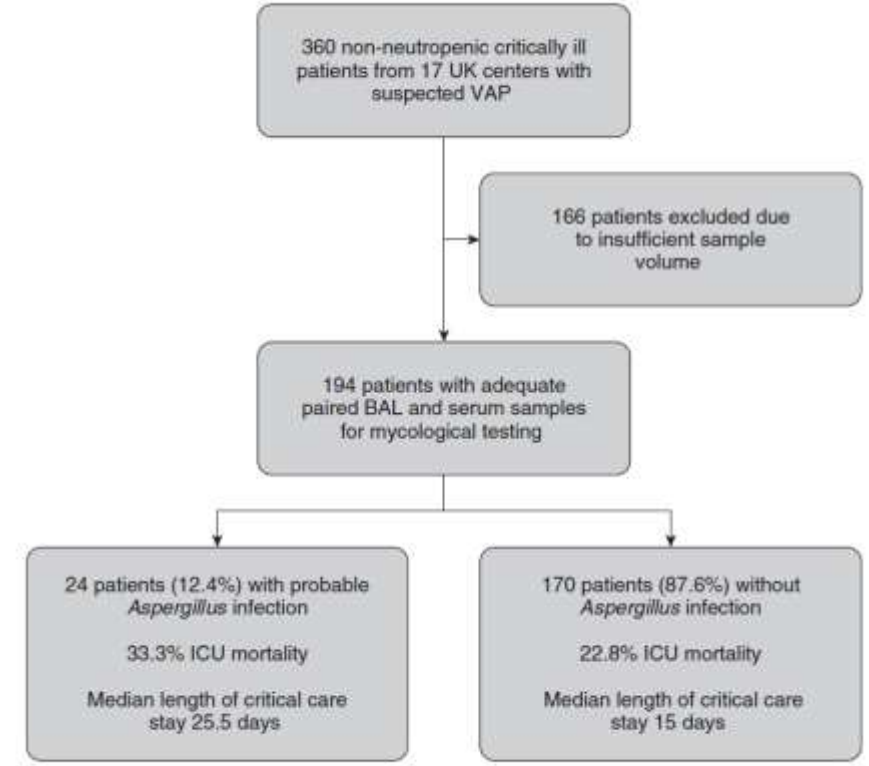


Figure 1. Study flow diagram. VAP = ventilator-associated pneumonia.

Criteria used - Modified Asp ICU 2018

1) Clinical criteria
2) Radiological criteria
3) Mycological criteria - Histopathology or direct microscopy or Positive Aspergillus culture from BALF. Or GM optical density (OD) index in BALF of >1 or GM OD index in serum of >0.5.

American Journal of Respiratory and Critical Care Medicine, 202(8), 1126-1138.

Table 1. Characteristics and Outcomes of Suspected VAP Patient Cohort

Characteristics	Suspected VAP Cohort (*n* = 194)	With Probable *Aspergillus* Infection (*n* = 24)	Without Probable *Aspergillus* Infection (*n* = 170)	*P* Value
Age, median (IQR), yr	57 (44–69)	66.5 (49.8-72.5)	56 (43–69)	0.07
Sex, M, *n* (%)	137 (70.6)	15 (62.5)	122 (71.8)	0.35
APACHE II score on admission, mean (SD)	17.93 (7.5)	19.25 (7.5)	17.74 (7.7)	0.36
Medical reason for admission, *n* (%)	113 (58.2)	17 (70.9)	96 (56.5)	0.18
Surgical reason for admission, *n* (%)	81 (41.8)	7 (29.1)	74 (43.5)	0.18
Preenrollment length of stay, median (IQR), d	7 (4–11)	7.5 (7–12)	6 (4–10.75)	0.19
Steroids, *n* (%)	33 (16.9)	6 (25)	27 (15.8)	0.27
WCC on day of BAL, *n*	15.3	14.95	15.3	0.83
Renal replacement therapy, *n* (%)	16 (8.3)	3 (12.5)	13 (7.7)	0.42
Vasopressors, *n* (%)	61 (31.4)	8 (33.3)	53 (31.2)	0.83
Microbiologically confirmed VAP, *n* (%)	78 (40.2)	9 (37.5)	69 (40.6)	0.77
Length of stay in critical care, median (IQR), d	17 (11–31.5)	25.5 (17.25–32.8)	15 (10–30.5)	0.02
Length of stay in hospital, median (IQR), d	34 (17–62)	34 (24.5-61)	34 (14.25–62)	0.39
ICU mortality, *n* (%)	47 (24.1)	8 (33.3)	39 (22.8)	0.27

BALF GM Threshold OD	Number of Patients with BALF Positive	Total Number of Aspergillosis Cases (BALF or Serum Positive)	Prevalence [% (95% CI)]
0.7	27	30	15.5 (10.7–21.3)
0.8	25	28	14.4 (9.8–20.2)
1.0	20	24	12.4 (8.1–17.8)
1.5	12	18	9.3 (5.6–14.3)
3.0	8	14	7.2 (4.0–11.8)

Definition of abbreviations: BALF = BAL fluid; CI = confidence interval; GM = galactomannan; OD = optical density.

American Journal of Respiratory and Critical Care Medicine, 202(8), 1126-1138.

EORTC/MSG criteria ICU working group - 2021

Proven IA : definitive evidence of filamentous growth plus associated tissue damage, confirmed by histopathology or culture .

Probable IA : Includes mycological evidence of Aspergillus spp. plus clinical/radiological abnormalities and host factors .

Host factors : Glucocorticoid treatment, chronic respiratory airway abnormality and decompensated cirrhosis, Haematological malignancies/HSCT, Human immunodeficiency virus infection, Severe influenza (or other severe viral pneumonia, such as coronavirus disease 2019 [COVID-19])

GM index >0.5 in blood or >0.7 in BALF

Bassetti, M. et al. (2021). Clinical Infectious Diseases, S121-S127

EORTC/MSG criteria

- Only relevant for a specific group of ICU patients, such as those with underlying hematological malignancies, solid organ transplant recipients, or those with severe immunosuppression.
- Very limited applicability in the ICU setting.

Bassetti, M. et al. (2021). Clinical Infectious Diseases, S121-S127

RESEARCH Open Access

New clinical algorithm including fungal biomarkers to better diagnose probable invasive pulmonary aspergillosis in ICU

BM - Asp ICU 2021

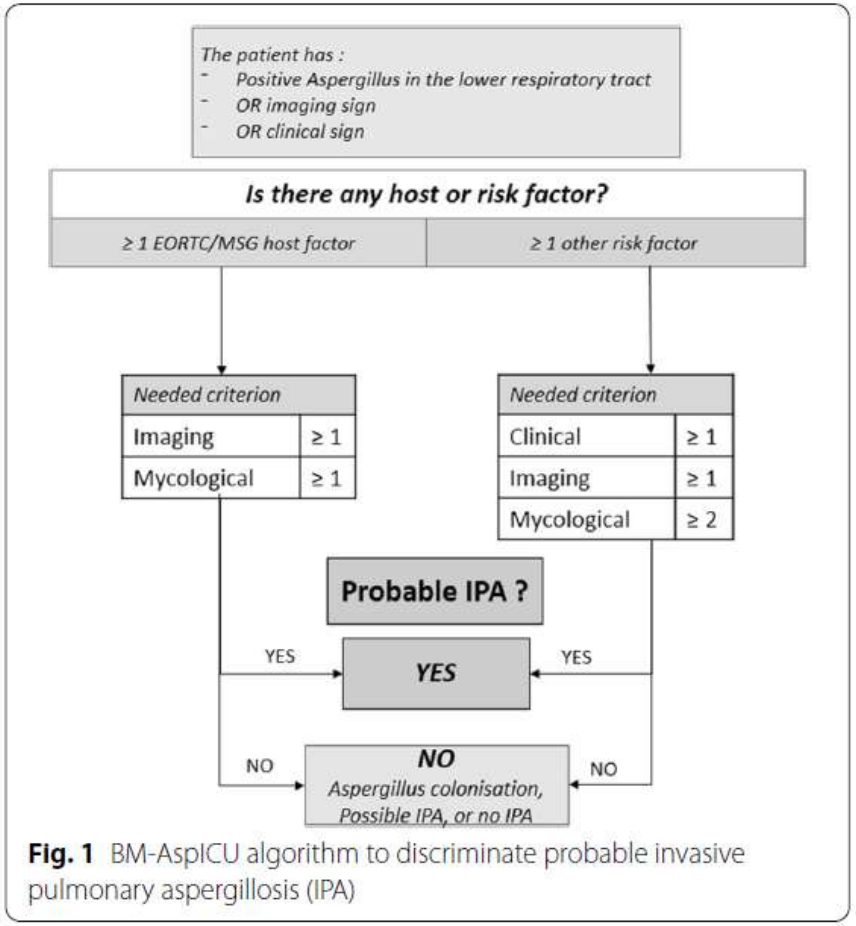


Fig. 1 BM-AspICU algorithm to discriminate probable invasive pulmonary aspergillosis (IPA)

Retrospective, multicenter design with data from the RESSIF network, focusing on ICU patients with suspected IPA. Data from 35 ICU

The BM-AspICU algorithm considers clinical signs, risk factors, radiological criteria, and mycological criteria, including GM antigen and Aspergillus qPCR, without pathology findings

Ann Intensive Care 2021 Mar 8;11(1):41

Table 1 Diagnostic criteria for invasive pulmonary aspergillosis according to EORTC/MSGERC-2008, EORTC/MSGERC-2019, AspICU and BM-AspICU

Criteria	EORTC/ MSGERC-2008	EORTC/ MSGERC-2019	AspICU	BM-AspICU
Host risk factors (immunosuppression)				
Neutropenia (< 500 neutrophils/mm^3 for > 10 days)	X	X	X	X
Receipt of an allogenic stem cell transplant	X	X	X	X
Corticosteroids > 0.3 mg/kg/day for > 3 weeks	X	X	X	X
Treatment with recognized T-cell immunosuppressant for more than 90 days	X	X	X	X
Inherited severe deficiency	X	X	X	X
Underlying hematological or oncological malignancy treated with cytotoxic agents	X	X	X	X
Ibrutinib treatment		X	X	X
Other risk factors				
Chronic obstructive pulmonary disease			X	X
Viral respiratory diseases (influenza infection, SARS-CoV2 infection, etc.)			X	X
Cirrhosis, hepatic insufficiency			X	X
Other (diabetes, chronic alcohol abuse, chronic diseases, cardiac surgery, etc.)			X	X
Clinical features				
Fever refractory to > 3 days of antibiotherapy			X	X
Pleuritic chest pain			X	X
Dyspnea			X	X
Hemoptysis			X	X
Respiratory insufficiency despite ventilation support			X	X
Imaging				
CT scan of the lung	X	X	X	X
Chest X-ray			X	X
Air-crescent sign	X	X	X	X
Cavity	X	X	X	X
Dense, well-circumscribed lesion(s) with or without halo sign	X	X	X	X
Diffuse reticular and alveolar opacities		X	X	X
Nonspecific infiltrates and consolidation		X	X	X
Pleural fluid			X	X
Wedge-shaped infiltrate		X	X	X
Tree-in-bud pattern			X	X
Mycological culture				
Positive direct examination showing hyphae	X	X	X	X
Positive *Aspergillus* culture in BALF	X	X	X	X
Positive *Aspergillus* culture in lower respiratory tract specimen	X	X	X	X
Fungal biomarkers				
BALF galactomannan	X	X		X
BALF *Aspergillus* qPCR		X*		X
Serum/plasma galactomannan	X	X		X
Serum/plasma *Aspergillus* qPCR		X*		X

* Two consecutive qPCR tests positive in blood, or one qPCR test positive in blood and one qPCR test positive in BALF

Category	Patients with EORTC/MSGERC Host Factors (n=11)	Patients without EORTC/MSGERC Host Factors (n=16)
Imaging Findings	Nodules, condensations, ground-glass opacities	Opacities, nodules, condensations, ground-glass
Positive Aspergillus Culture	6 (54.5%)	13 (81.3%)
Positive Serum GM	4	8
Positive BALF GM	3	5
AspICU Classification	9 Putative, 2 Not sortable	11 Putative, 5 Not sortable
BM-AspICU Classification	11 Probable	14 Probable, 2 Not sortable
Mortality Rate	6 (54.5%)	12 (75%)

Ann Intensive Care 2021 Mar 8;11(1):41

- BM-AspICU identified 24 probable IPA cases, compared to 16 by AspICU, by including Aspergillus qPCR and GM antigen detection.
- It uses broader microbiological and imaging criteria suitable for ICU patients, even without immunosuppression.
- This approach aligns with updated guidelines (ESCMID-ECMM-ERS, ATS, EORTC/MSGERC-2019).
- The AspICU algorithm lacked fungal biomarkers, relying solely on Aspergillus-positive BALF culture and hyphae detection, missing cases without host risk factors.
- Its retrospective design , absence of control group ,lack of autopsy confirmation prospective validation is needed to confirm its accuracy and utility in ICU settings.

Ann Intensive Care 2021 Mar 8;11(1):41

CONFERENCE REPORTS AND EXPERT PANEL

Invasive Fungal Diseases in Adult Patients in Intensive Care Unit (FUNDICU): 2024 consensus definitions from ESGCIP, EFISG, ESICM, ECMM, MSGERC, ISAC, and ISHAM

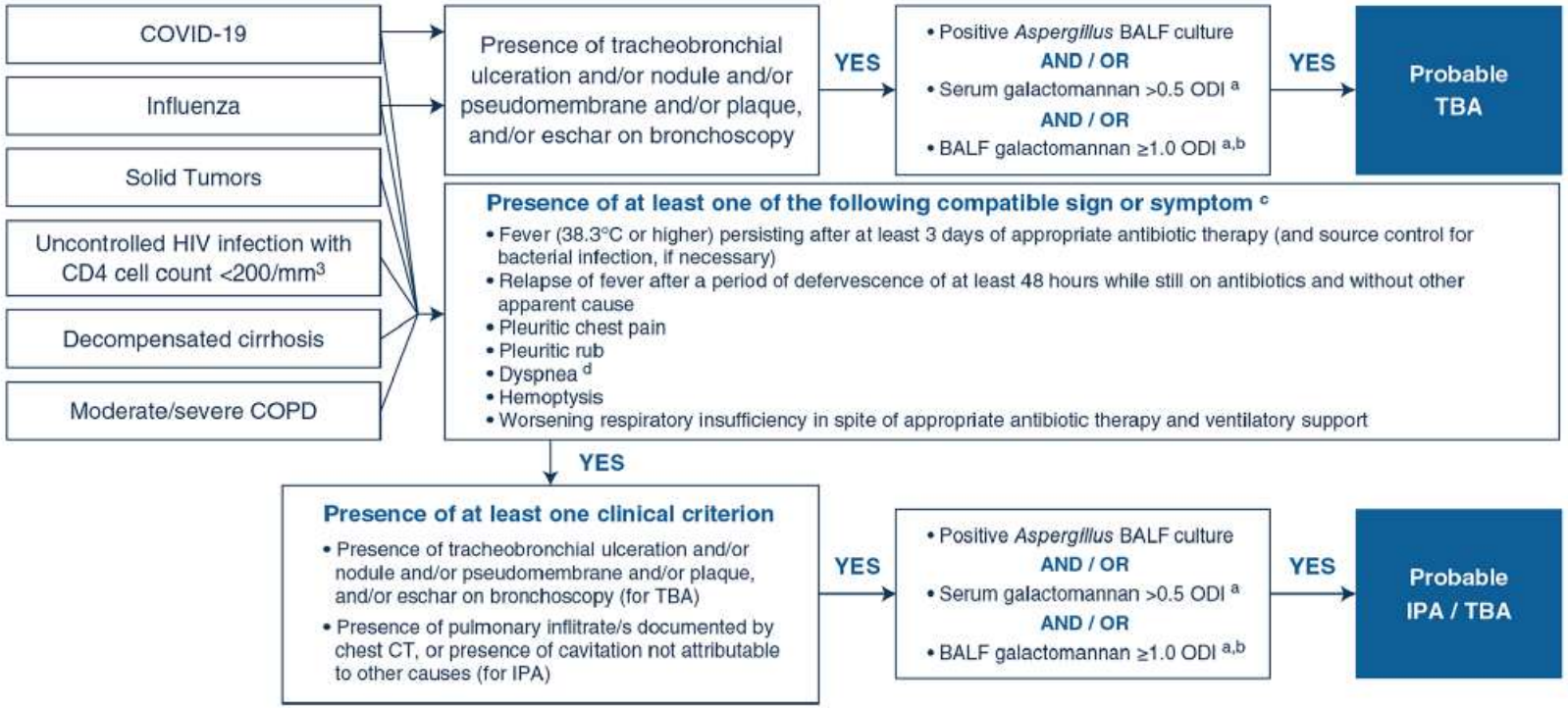
FUNDICU 2024

Research definition for proven invasive aspergillosis in non-neutropenic, adult patients in ICU

Definition of proven invasive aspergillosis
Consensus reached after two rounds of remote voting and one round of live meeting voting (93% agreement)
Proven invasive aspergillosis is defined by at least one of the following
Tissue invasion shown by histological or cytopathological evidence on a specimen obtained from a normally sterile site or the lung with biopsy or needle aspiration, combined with detection of hyphae compatible with *Aspergillus* spp. (confirmed by culture or PCR)
Recovery of *Aspergillus* spp. by culture on a specimen obtained from a normally sterile site by means of biopsy or needle aspiration, from a lesion consistent with an infectious process

Bassetti, M. et al. (2024). Intensive Care Medicine, 50(4), 502-515

Flowchart of Probable IPA and TBA in non neutropenic adult patients in ICU



Bassetti, M. et al. (2024). Intensive Care Medicine, 50(4), 502-515

DIAGNOSTICS

GALACTOMANNAN

Whom to test ?

- Neutrophils scavenge galactomannan hence serum GM has very low sensitivity in non neutropenic patient

Serum GMI

- Neutropenic
- Hematologic malignancy
- Not on anti mold prophylaxis

Bal GMI

- Solid organ transplant recipients
- Non neutropenic immunosuppressed patients

Cochrane Library

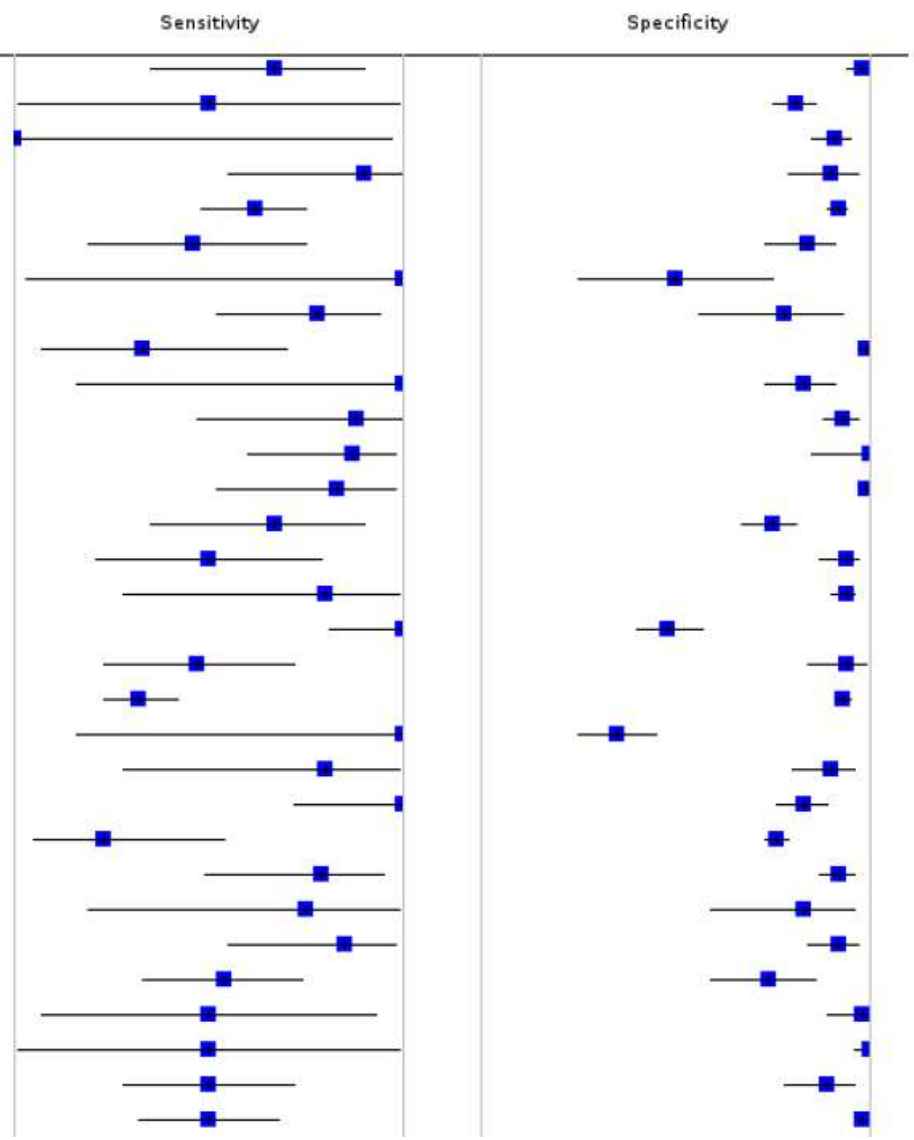
Cochrane Database of Systematic Reviews

Galactomannan detection for invasive aspergillosis in immunocompromised patients (Review)

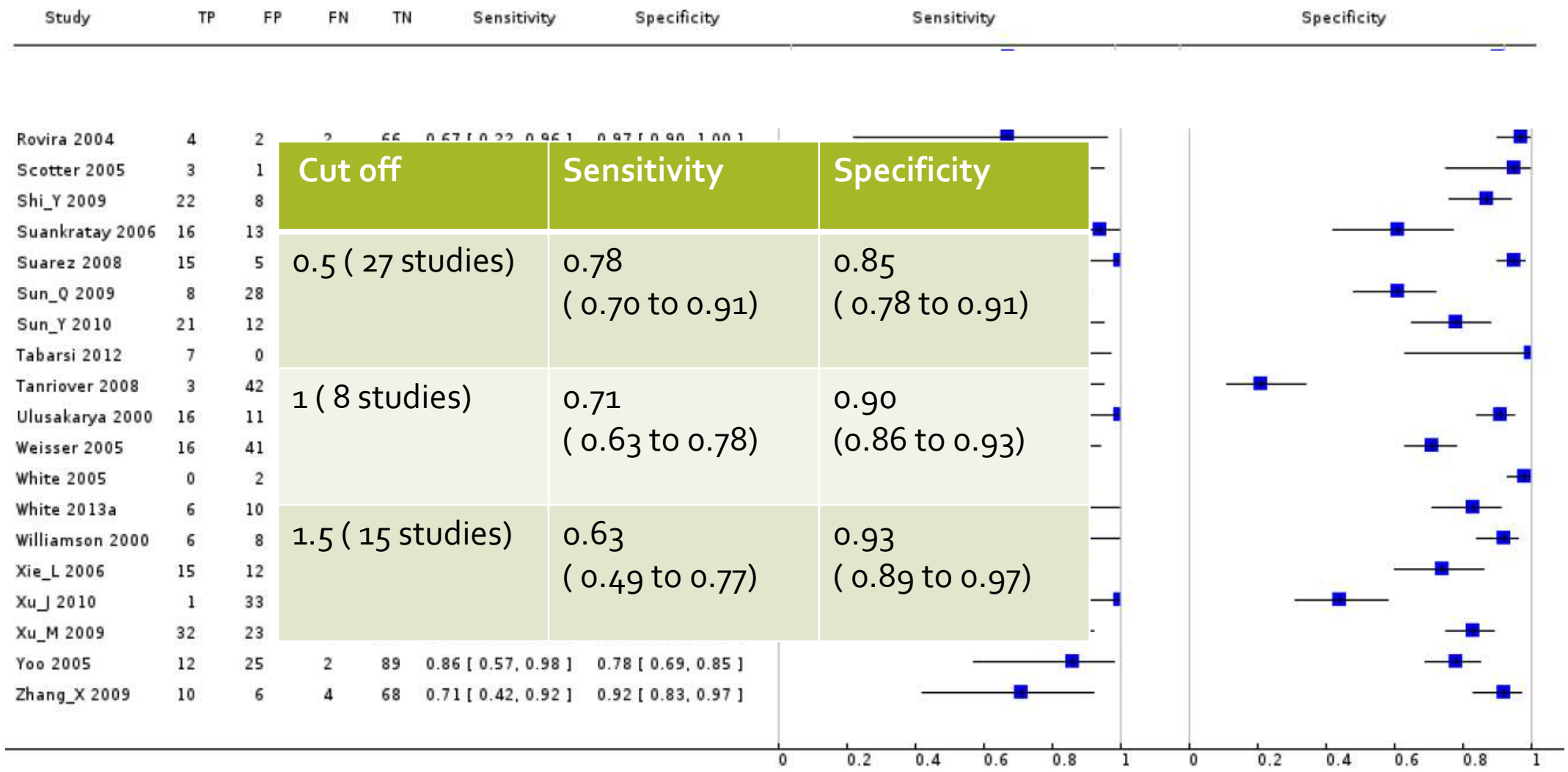
Leeflang MMG, Debets-Ossenkopp YJ, Wang J, Visser CE, Scholten RJPM, Hooft L, Bijlmer HA, Reitsma JB, Zhang M, Bossuyt PMM, Vandenbroucke-Grauls CM

Review: Galactomannan detection for invasive aspergillosis in immunocompromised patients
Test: 1 Platelia - all cut-offs

Study	TP	FP	FN	TN	Sensitivity	Specificity
Acosta 2012	8	4	4	168	0.67 [0.35, 0.90]	0.98 [0.94, 0.99]
Adam 2004	1	41	1	175	0.50 [0.01, 0.99]	0.81 [0.75, 0.86]
Allan 2005	0	11	1	113	0.0 [0.0, 0.97]	0.91 [0.85, 0.95]
Badiee 2013	9	5	1	47	0.90 [0.55, 1.00]	0.90 [0.79, 0.97]
Barnes 2013	33	39	20	457	0.62 [0.48, 0.75]	0.92 [0.89, 0.94]
Becker 2003	6	12	7	62	0.46 [0.19, 0.75]	0.84 [0.73, 0.91]
Bialek 2002	1	8	0	8	1.00 [0.03, 1.00]	0.50 [0.25, 0.75]
Bretagne 1998	14	5	4	18	0.78 [0.52, 0.94]	0.78 [0.56, 0.93]
Buchheidt 2004	3	1	6	167	0.33 [0.07, 0.70]	0.99 [0.97, 1.00]
Busca 2006	2	12	0	60	1.00 [0.16, 1.00]	0.83 [0.73, 0.91]
Da Silva 2010	7	11	1	150	0.88 [0.47, 1.00]	0.93 [0.88, 0.97]
De Mol 2013	13	0	2	23	0.87 [0.60, 0.98]	1.00 [0.85, 1.00]
Doermann 2002	10	4	2	407	0.83 [0.52, 0.98]	0.99 [0.98, 1.00]
Florent 2006	8	39	4	116	0.67 [0.35, 0.90]	0.75 [0.67, 0.81]
Foy 2007	6	7	6	102	0.50 [0.21, 0.79]	0.94 [0.87, 0.97]
Gao 2010	4	16	1	240	0.80 [0.28, 0.99]	0.94 [0.90, 0.96]
Ghosh 2013	18	68	0	64	1.00 [0.81, 1.00]	0.48 [0.40, 0.57]
He 2011a	8	3	9	49	0.47 [0.23, 0.72]	0.94 [0.84, 0.99]
Herbrecht 2002	31	49	67	650	0.32 [0.23, 0.42]	0.93 [0.91, 0.95]
Jha 2013	2	64	0	34	1.00 [0.16, 1.00]	0.35 [0.25, 0.45]
Kallel 2003	4	7	1	62	0.80 [0.28, 0.99]	0.90 [0.80, 0.96]
Kawazu 2004	11	23	0	115	1.00 [0.72, 1.00]	0.83 [0.76, 0.89]
Ku 2012	3	183	10	582	0.23 [0.05, 0.54]	0.76 [0.73, 0.79]
Lai 2007	11	14	3	161	0.79 [0.49, 0.95]	0.92 [0.87, 0.96]
Machetti 1998	3	3	1	15	0.75 [0.19, 0.99]	0.83 [0.59, 0.96]
Maertens 2002	11	7	2	80	0.85 [0.55, 0.98]	0.92 [0.84, 0.97]
Marr 2004	13	11	11	32	0.54 [0.33, 0.74]	0.74 [0.59, 0.86]
Moragues 2003	2	1	2	49	0.50 [0.07, 0.93]	0.98 [0.89, 1.00]
Nihtinen 2010	1	0	1	100	0.50 [0.01, 0.99]	1.00 [0.96, 1.00]
Park 2010	11	6	11	51	0.50 [0.28, 0.72]	0.89 [0.78, 0.96]
Pinel 2003	17	17	17	756	0.50 [0.32, 0.68]	0.98 [0.97, 0.99]



Review: Galactomannan detection for invasive aspergillosis in immunocompromised patients
Test: 1 Platelia - all cut-offs



Cut off	Sensitivity	Specificity
0.5 (27 studies)	0.78 (0.70 to 0.91)	0.85 (0.78 to 0.91)
1 (8 studies)	0.71 (0.63 to 0.78)	0.90 (0.86 to 0.93)
1.5 (15 studies)	0.63 (0.49 to 0.77)	0.93 (0.89 to 0.97)

Cochrane Library

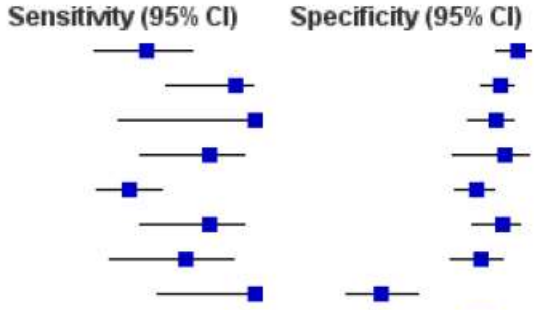
Cochrane Database of Systematic Reviews

Galactomannan detection in broncho-alveolar lavage fluid for invasive aspergillosis in immunocompromised patients (Review)

de Heer K, Gerritsen MG, Visser CE, Leeflang MMG

ODI 0.5

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bergeron 2010	17	5	12	67	0.59 [0.39, 0.76]	0.93 [0.85, 0.98]
Brownback 2013	13	18	1	111	0.93 [0.66, 1.00]	0.86 [0.79, 0.92]
Clancy 2007	5	12	0	64	1.00 [0.48, 1.00]	0.84 [0.74, 0.92]
de Mol 2013	14	3	3	21	0.82 [0.57, 0.96]	0.88 [0.68, 0.97]
Fisher 2014	35	33	32	110	0.52 [0.40, 0.65]	0.77 [0.69, 0.84]
Hoenigl 2014	14	8	3	53	0.82 [0.57, 0.96]	0.87 [0.76, 0.94]
Nguyen 2011	11	15	4	54	0.73 [0.45, 0.92]	0.78 [0.67, 0.87]
Pasqualotto 2010	8	31	0	21	1.00 [0.63, 1.00]	0.40 [0.27, 0.55]
Penack 2008	17	6	0	22	1.00 [0.8	
Prattes 2014	18	23	1	47	0.95 [0.7	
Prattes 2015	5	4	2	61	0.71 [0.2	
Rose 2014	10	6	4	99	0.71 [0.4	

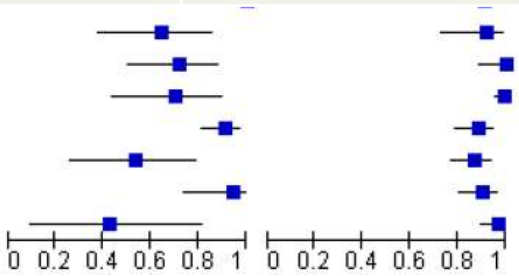


ODI 0.85 and 0.87

Study	TP	FP	FN	TN	Sensitivity (95% CI)	S
de Mol 2013	11	2	6	22	0.65 [0.38, 0.86]	
Nguyen 2011	10	11	5	58	0.67 [0.38, 0.88]	
Prattes 2014	18	8	1	62	0.95 [0.74, 1.00]	
Prattes 2015	4	3	3	62	0.57 [0.18, 0.90]	

ODI 1.0

Study	TP	FP	FN	TN	Sensitivity (95
Becker 2003 -- part I	7	3	0	20	1.00 [0.59,
Becker 2003 -- part II	11	11	1	34	0.92 [0.62,
Brownback 2013	9	7	5	122	0.64 [0.35,
Clancy 2007	5	7	0	69	1.00 [0.48,
de Mol 2013	11	2	6	22	0.65 [0.38, 0.86]
Frealle 2009	18	0	7	32	0.72 [0.51, 0.88]
Hoenigl 2014	12	1	5	111	0.71 [0.44, 0.90]
Maertens 2009	53	8	5	62	0.91 [0.81, 0.97]
Nguyen 2011	8	9	7	60	0.53 [0.27, 0.79]
Prattes 2014	18	7	1	63	0.95 [0.74, 1.00]
Prattes 2015	3	2	4	63	0.43 [0.10, 0.82]



Cut off	Sensitivity	Specificity
0.5 (12 studies)	0.88 (0.75 to 1)	0.81 (0.71 to 0.91)
1 (11 studies)	0.78 (95% CI 0.61 to 0.95)	0.93 (95% CI 0.87 to 0.98)

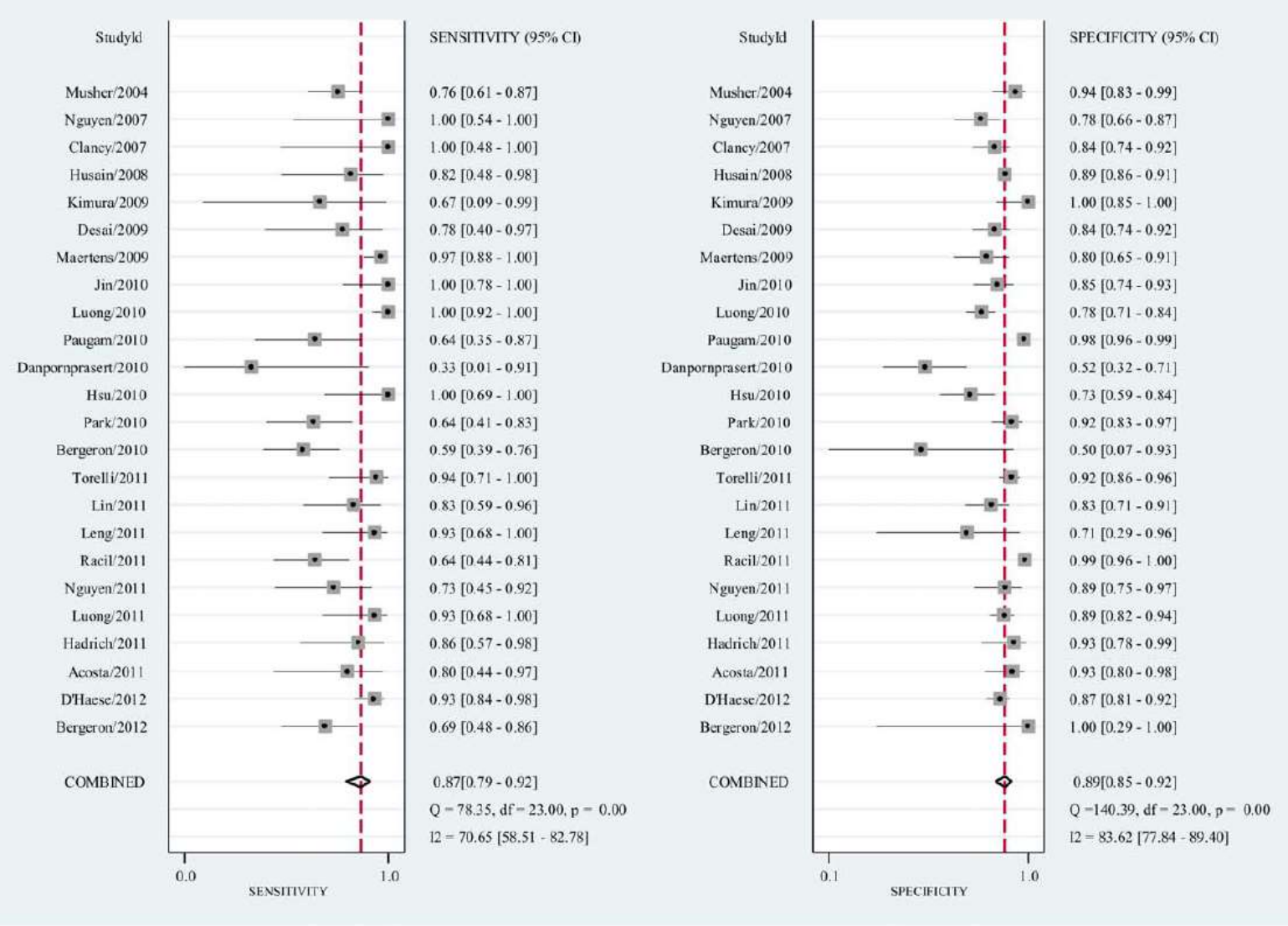
Systematic Review and Meta-Analysis of Detecting Galactomannan in Bronchoalveolar Lavage Fluid for Diagnosing Invasive *Aspergillosis*

Mingxiang Zou[1☯], Lanhua Tang[2☯], Shushan Zhao[2*], Zijin Zhao[2], Luyao Chen[2], Peng Chen[3], Zebing Huang[4], Jun Li[1], Lizhang Chen[5], Xuegong Fan[4]

- Objective: To evaluate the overall diagnostic accuracy of bronchoalveolar lavage (BAL) galactomannan (GM)
- Method: Systematic review of 30 diagnostic studies (24 cohort and 6 case control) till 2012
- Cutoff Values: Analysis conducted for BAL-GM cutoff values of 0.5 and 1.0
- Studies evaluated BAL GM for diagnosing IA using EORTC /MSG criteria 2002/2008
- Patient population not explicated

PLoS ONE. 2012;7(8):e43347.

Forest plot of sensitivities and specificities from test accuracy studies of BAL-GM in the diagnosis of IA.



- Pooled Sensitivity: 0.87 (95% Confidence Interval (CI) 0.79–0.92) for diagnosing proven or probable invasive aspergillosis (IA) using a cutoff value of 0.5.
- Pooled specificity of the BAL-GM assay was 0.89 (95% CI 0.85–0.92).

PLoS ONE. 2012;7(8):e43347.

. Pooled results of the included studies for IA.

Comparison	Cutoff	Studies	DOR (95% CI)	AUC (95% CI)	SEN*Heterogeneity* (p/I^2)	Pooled SEN (95% CI)	SPE*Heterogeneity* (p/I^2)	Pooled SPE (95% CI)
Proven or probable IA vs. possible or no IA	0.5	24	52.7 (31.8–87.3)	0.94	<0.01/70.65	0.87 (0.79–0.92)	<0.01/83.20	0.89(0.85–0.92)
	1.0	21	112.7 (55.9–227.1)	0.97	<0.01/79.00	0.86 (0.76–0.92)	<0.01/89.04	0.95(0.91–0.97)
	1.5	10	143.4 (51.4–400.4)	0.97	<0.01/77.88	0.85 (0.71–0.96)	<0.01/79.41	0.95(0.90–0.97)
	2.0	8	97.4 (35.0–270.9)	0.96	<0.01/73.26	0.84 (0.65–0.94)	0.61/0	0.95(0.93–0.96)
	2.5	6	79.9 (20.5–311.7)	0.96	<0.01/81.30	0.80 (0.50–0.94)	0.89/0	0.95(0.93–0.97)

At a cutoff of **0.5**, the BAL-GM assay had a sensitivity of 0.87 and specificity of 0.89, changing the cutoff to **1.0,** the specificity improved to 0.95, while sensitivity remained at 0.86.

PLoS ONE. 2012;7(8):e43347.

Research Article

Galactomannan in Bronchoalveolar Lavage Fluid for Diagnosis of Invasive Pulmonary Aspergillosis with Nonneutropenic Patients

- Retrospective cohort study reviewed nonneutropenic patients from April 2014 to February 2017.
- The study included 183 patients in the final analysis, with 10 diagnosed with probable IPA and none with proven IPA and 21 possible IPA
- Bronchoscopies were performed, and BALF samples were collected for direct microscopic examination, microbiological culture, and GM detection using the Platelia Aspergillus EIA (Bio-Rad) .
- IPA cases were classified according to the EORTC/MSG criteria 2008

Can Respir J. 2017 Nov 13;2017:3685261

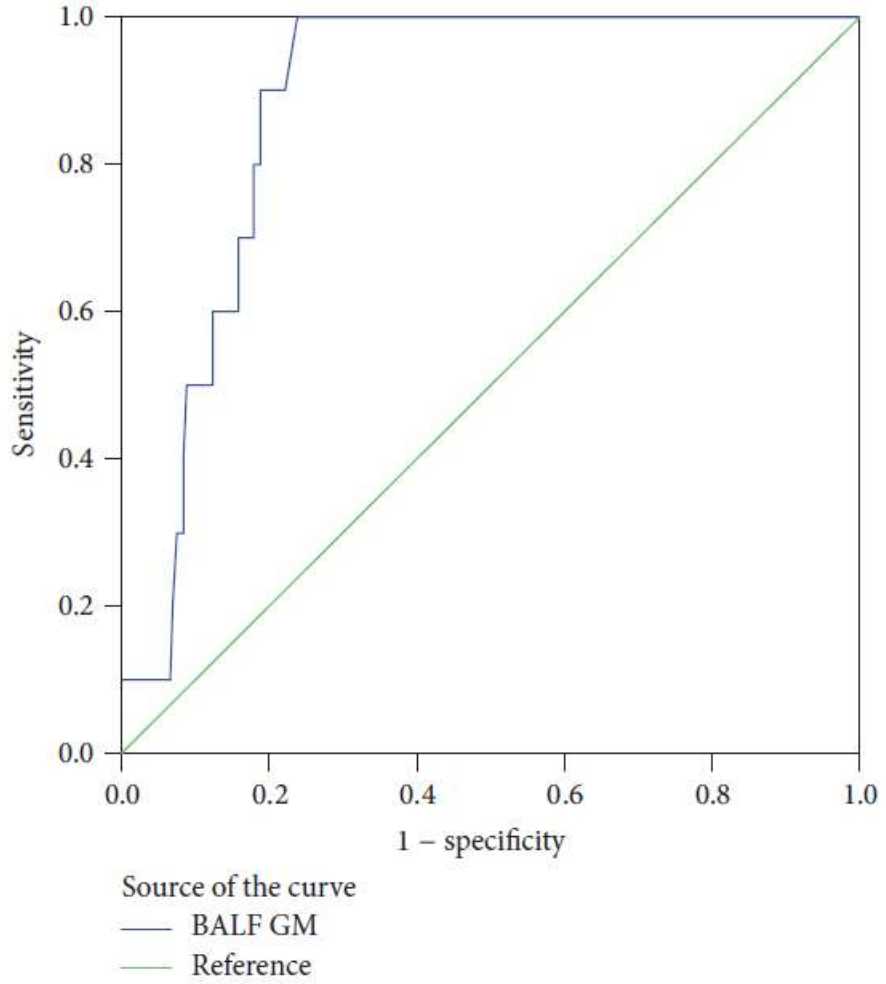
Research Article

Galactomannan in Bronchoalveolar Lavage Fluid for Diagnosis of Invasive Pulmonary Aspergillosis with Nonneutropenic Patients

Performance of GM detection for diagnosis of IPA in BALF.

Cutoff value	Sensitivity%	Specificity%	PPV%	NPV%
BALF GM ≥ 0.5	100.0%	64.3%	16.4%	100.0%
BALF GM ≥ 0.76	100.0%	76.2%	22.7%	100.0%
BALF GM ≥ 0.8	90.0%	78.3%	22.5%	99.1%
BALF GM ≥ 1.0	70.0%	82.5%	21.9%	97.5%
BALF GM ≥ 1.5	60.0%	86.0%	23.1%	96.8%
BALF GM ≥ 2.0	50.0%	88.8%	23.8%	96.2%

- GM in BALF of 0.76 and 1.0 yielded a sensitivity of 100.0% , 70% and a specificity of 76.2% and 82.5% respectively



Receiver operating characteristic (ROC) curves for galactomannan assay in 183 study populations. Areas under the ROC curve was 0.88 (95% CI 0.82–0.94).

Can Respir J. 2017 Nov 13;2017:3685261

Risk factors for false-positive galactomannan results in bronchoalveolar lavage assays with univariate analysis and logistic regression analysis, respective

Variables	Case patients[a] (n = 30), n (%)	Control patients[b] (n = 113), n (%)	p	
			Univariate analysis	Logistic regression analysis
Age ≥ 60 years	12 (40.0)	51 (45.1)	0.615	0.533
Male gender	13 (43.3)	64 (56.6)	0.194	0.067
Seasonal distribution				
March–October	23 (76.7)	70 (61.9)	0.133	0.129
Underlying disease				
Emphysema	2 (6.7)	10 (8.8)	0.990	0.608
COPD	3 (10.0)	5 (4.4)	0.463	0.121
Bronchial asthma	2 (6.7)	5 (4.4)	0.976	0.273
Pulmonary tuberculosis	7 (23.3)	10 (8.8)	0.063	0.117
Solid tumor	0	11 (9.7)	0.164	0.999
Bronchiectasis	7 (23.3)	16 (14.2)	0.349	0.431
Diabetes	0	11 (9.7)	0.164	0.999
Liver cirrhosis	0	1 (0.9)	1.000	0.999
Hematologic malignancy	0	1 (0.9)	1.000	1.000
Autoimmune disease	0	2 (1.8)	1.000	0.999
Kidney non-malignant disease	1 (3.3)	1 (0.9)	0.377	1.000
Antibiotics				
Piperacillin/tazobactam	9 (30.0)	22 (19.5)	0.213	0.479
Mezlocillin/sulbactam	2 (6.7)	5 (4.4)	0.976	0.726
Cephalosporins	7 (23.3)	49 (43.4)	0.046	0.157
Quinolones	7 (23.3)	37 (32.7)	0.321	0.404

No significant difference among two groups

Piperacillin/tazobactam did not show significant differences in false positives compared to controls

Can Respir J. 2017 Nov 13;2017:3685261

Defining Galactomannan Positivity in the Updated EORTC/MSGERC Consensus Definitions of Invasive Fungal Diseases

Toine Mercier,[1,2] Elio Castagnola,[3] Kieren A. Marr,[4] L. Joseph Wheat,[5] Paul E. Verweij,[6] and Johan A. Maertens[1,2]

[1]Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium, [2]Department of Hematology, University Hospitals Leuven, Leuven, Belgium, [3]Infectious Diseases Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy, [4]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA, [5]MiraVista Diagnostics, Indianapolis, Indiana, USA, and [6]Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, The Netherlands

Table 1. Summary of Meta-analyses of the Performance of Galactomannan in Serum or Plasma in Different Subgroups

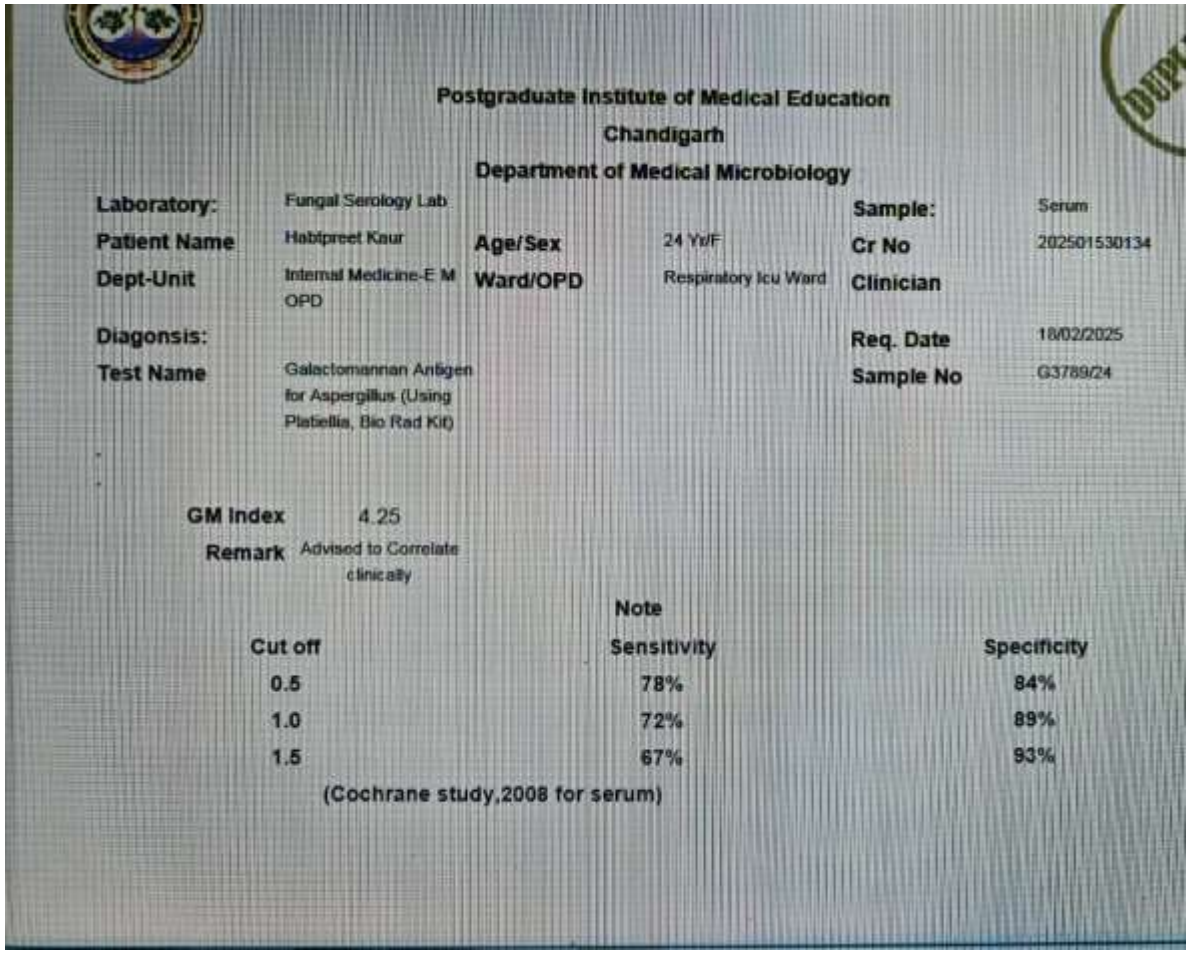
Subgroup	Sensitivity	Specificity	PLR	NLR
Cutoff				
0.5 ODI	0.78–0.79	0.85–0.86	5.20–5.64	0.24–0.26
1.0 ODI	0.65–0.71	0.90–0.94	6.50–11.83	0.31–0.39
1.5 ODI	0.48–0.63	0.93–0.95	6.86–12.60	0.39–0.56
Population				
HM	0.58	0.95	11.60	0.44
HSCT	0.65	0.65	1.86	0.54
SOT	0.41	0.85	2.73	0.69

Combined cut off serum 0.7 and BAL 0.8 : This strategy has not been investigated in specific clinical trials ,based on consensus among practitioners.

Summary of Meta-analyses of the Performance of Galactomannan in Bronchoalveolar Lavage Fluid in Different Subgroups

Subgroup	Sensitivity	Specificity	PLR
Cutoff			
0.5 ODI	0.82–0.87	0.89–0.92	7.45–10.88
1.0 ODI	0.75–0.86	0.94–0.95	12.50–17.20
1.5 ODI	0.70–0.92	0.95–0.98	14.00–46.00
2.0 ODI	0.61–0.84	0.95–0.96	12.20–21.00
Hematologic malignancy			
Yes	0.85	0.91	9.44
No	0.87	0.89	7.91

Clinical Infectious Diseases. 2021;72:S89–94



Postgraduate Institute of Medical Education
Chandigarh
Department of Medical Microbiology

Laboratory:	Fungal Serology Lab			Sample:	Serum
Patient Name	Habtpreet Kaur	Age/Sex	24 Yr/F	Cr No	202501530134
Dept-Unit	Internal Medicine-E M OPD	Ward/OPD	Respiratory Icu Ward	Clinician	
Diagonsis:				Req. Date	18/02/2025
Test Name	Galactomannan Antigen for Aspergillus (Using Platiellia, Bio Rad Kit)			Sample No	G3789/24

GM Index 4.25
Remark Advised to Correlate clinically

Note

Cut off	Sensitivity	Specificity
0.5	78%	84%
1.0	72%	89%
1.5	67%	93%

(Cochrane study,2008 for serum)

Galactomannan detection for invasive aspergillosis in immunocompromized patients (Review)

Leeflang MM, Debets-Ossenkopp YJ, Visser CE, Scholten RJPM, Hooft L, Bijlmer HA, Reitsma JB, Bossuyt PMM, Vandenbroucke-Grauls CM

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 4

http://www.thecochranelibrary.com

Aspergillus PCR in serum for the diagnosis, follow-up and prognosis of invasive aspergillosis in neutropenic and nonneutropenic patients

S. Imbert[1], L. Gauthier[1], I. Joly[1], J.-Y. Brossas[3], M. Uzunov[2], F. Touafek[1], S. Brun[1], D. Mazier[1,3,4], A. Datry[1], F. Gay[1,4] and A. Fekkar[1,3,4]

- Retrospective single-centre study conducted at Paris from February 2012 to October 2014.
- Participants:941 patients at risk of IA, with 5146 serum samples analysed.
- Categorized into neutropenic and non-neutropenic groups.
- A real-time PCR was used, targeting a 67 bp segment of 28S ribosomal RNA coding DNA
- Criteria for IA Classification: Extended EORTC/MSG criteria extended to include alcoholic liver cirrhosis, ICU stay, and severe ARDS as host factors

Clin Microbiol Infect. 2016;22:562.e1–562.e8.

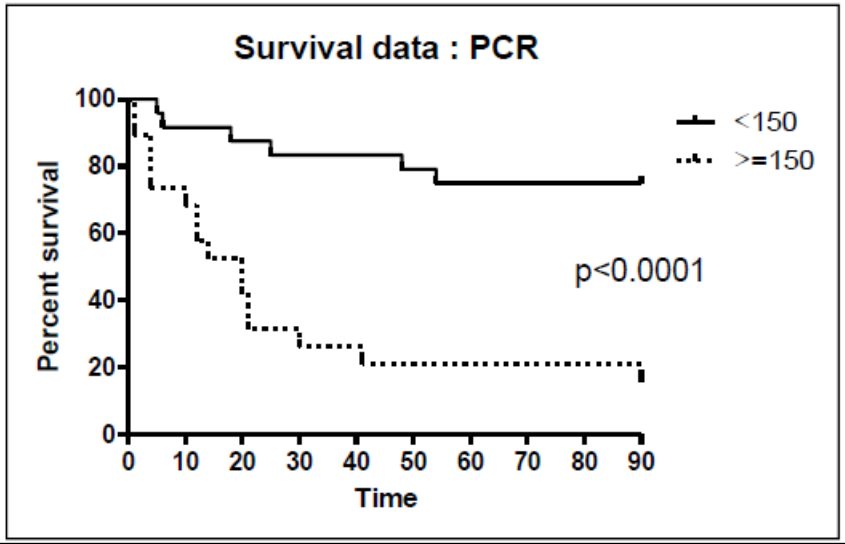
Performance of PCR to detect *Aspergillus fumigatus* in serum, determination of galactomannan index in serum and mycologic examination of respiratory samples for the diagnosis of invasive aspergillosis in 60 patients treated for proven/probable invasive aspergillosis according to extended EORTC/MSG criteria with the addition of PCR in the mycologic criteria

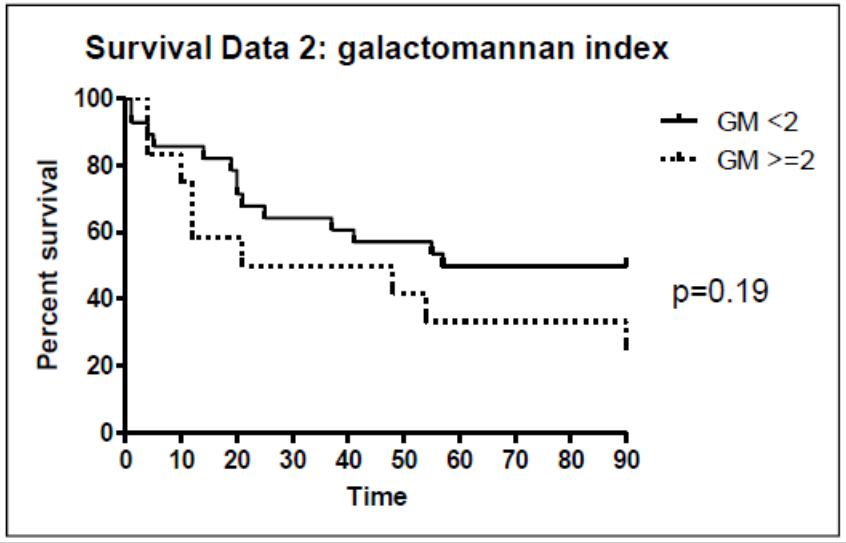
Method	Neutrophil status	Group	No. of samples with result		Sensitivity	Specificity	Positive predictive value	Negative predictive value	p[b]	
			Positive	Negative						
Galactomannan	All patients	IA[a]	40	20	66.7	87.7	27	97.5		
		Non-IA	108	773						
	Neutropenic	IA	19	9	67.8	83.9	22	97.5	0.93	Compared to nonneutropenic
		Non-IA	67	350					<0.005	Compared to nonneutropenic
	Nonneutropenic	IA	21	11	65.6	91.2	33.9	97.5		
		Non-IA	41	423						
Mycologic examination	All patients	IA	32	14	69.6	NA	NA	NA		
	Neutropenic		8	9	47					
	Nonneutropenic		24	5	82.7					
PCR	All patients	IA	43	17	71.7	98.8	79.6	98		
		Non-IA	11	870						
	Neutropenic	IA	23	5	82.1	98.1	74.2	98.8	0.09	Compared to nonneutropenic
		Non-IA	8	409					0.09	Compared to nonneutropenic
	Nonneutropenic	IA	20	12	62.5	99.4	87	97.5		
		Non-IA	3	461						

EORTC/MSG, European Organization for Research and Treatment of Cancer/Mycosis Study Group; IA, invasive aspergillosis; NA, not available.
[a]Criteria used for classification of IA were those defined jointly by the EORTC/MSG consensus and published in 2008 with additionally inclusion of PCR as a mycologic criteria and minor modifications for host factors (e.g. inclusion of alcoholic liver cirrhosis).
[b]As calculated by chi-square test between neutropenic and nonneutropenic patients

- Aspergillus PCR - Highest sensitivity (71.7%) and specificity (98.8%) among all patients
- PCR was effective in neutropenic patients, with a statistically significant improvement in sensitivity ($p < 0.005$).

Clin Microbiol Infect. 2016;22:562.e1–562.e8.





These findings supported the inclusion of PCR in EORTC/MSG criteria (2021) to enhance IA classification

Marker	Cutoff Value	Survival Rate (%)	p-value	Hazard Ratio (95% CI)	Conclusion
PCR Fungal Load	<150 copies/mL	73.2%	<0.0001	0.14 (0.05–0.34)	Significantly better survival
	≥150 copies/mL	15.8%			High risk of mortality
GM Index	<2.0	50%	0.19	0.5 (0.20–1.29)	No significant difference
	≥2.0	25%			

Clin Microbiol Infect. 2016;22:562.e1–562.e8.

Detection of *Pneumocystis jirovecii* and *Aspergillus* spp. DNA in bronchoalveolar lavage fluids by commercial real-time PCR assays: comparison with conventional diagnostic tests

Aspergillus PCR in BAL

- Prospective Study conducted from September 2011 to December 2012 at Italy.
- 44 bronchoalveolar lavage (BAL) fluids collected from 41 patients at high risk for invasive fungal diseases (IFD).
- Patients were grouped into: Pneumocystis jirovecii pneumonia (PCP) group (n = 8) Invasive Aspergillosis (IA) group (n = 10) Control group (n = 24)

Performance of Diagnostic Tests:

Method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
ASP-PCR	80.0	97.1	88.9	94.3	0.89
GM Assay	100	92.3	87.0	100	Not Given
BAL Culture	60.0	100	100	80.0	Not Given

Comparison Between Assays:

Diagnostic Method	Positive in IA Group (n=10)	False Positives in Non-IA Group (n=34)
ASP-PCR	8/10 (80%)	1/34 (2.9%)
GM Assay	10/10 (100%)	3/34 (8.8%)
BAL Culture	6/10 (60%)	0/34 (0%)

New Microbiol.2015 Jan;38(1):75-84. Epub 2015 Jan 1

- Small sample size of only 44 BAL samples from 41 patients were analyzed
- Lack of gold standard confirmation: proven IA cases were not confirmed by histopathology or autopsy.
- Lack of standardization: variability in collection techniques
- Standardized protocols are needed to reduce variability and improve reproducibility.
- Single assay platform was evaluated, limiting the comparison with other PCR platforms.

New Microbiol.2015 Jan;38(1):75-84. Epub 2015 Jan 1

Diagnosis of invasive pulmonary aspergillosis by lateral flow assay of galactomannan in bronchoalveolar lavage fluid: a meta-analysis of diagnostic performance

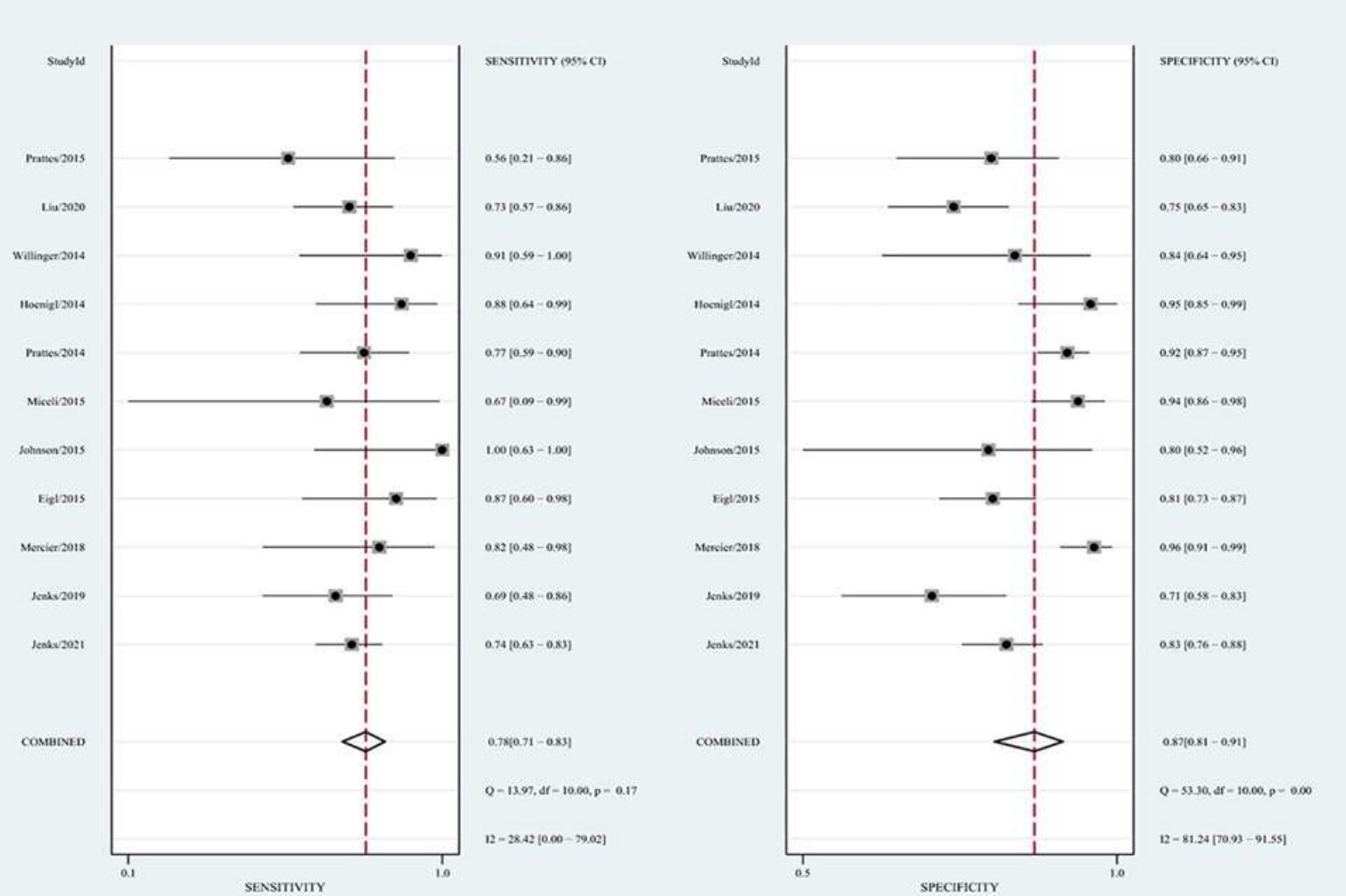
Yingli Cai[1,2], Jun Liang[1,2], Guangsheng Lu[1], Yankun Zhan[1], Jianwei Meng[1], Zhusheng Liu[1], Yiming Shao[2,*]

- Meta-analysis - 11 studies , observational studies (6 retrospective and 5 prospective studies) on the use of LFA for IPA diagnosis in BALF samples till July 2022
- Used different criteria : EORTC/MSG in 2002, 2008, 2019 and Blot et al 2012
- Studies examined BALF samples from patients with suspected or confirmed IPA using Aspergillus galactomannan LFA as a rapid diagnostic test were included

Letters in Applied Microbiology. 2023;76:1–7

Diagnosis of invasive pulmonary aspergillosis by lateral flow assay of galactomannan in bronchoalveolar lavage fluid: a meta-analysis of diagnostic performance

Yingli Cai[1,2], Jun Liang[1,2], Guangsheng Lu[1], Yankun Zhan[1], Jianwei Meng[1], Zhusheng Liu[1], Yiming Shao[2,*]



Category	Sensitivity [95% CI]	Specificity [95% CI]
IPA	0.78 [0.71, 0.83]	0.87 [0.81, 0.91]

- Small sample size , based on observational studies
- Study population - predominant haematological malignancy

Letters in Applied Microbiology. 2023;76:1–7

Comparison of the Equivalence of *Aspergillus* Antigen and PCR Results Between Non-Directed Bronchial Lavage and Bronchoalveolar Lavage—A Prospective Exploratory Pilot Study in Critically Ill Patients

Maria Schroeder[1] | Mohamad Abd Raboh[1] | Annika Nuechtern[1] | Dominic Wichmann[1] | Johannes Stamm[1] | Tim Hardel[1] | Holger Rohde[2] | Martin Christner[2] | Ann-Kathrin Ozga[3] | Stefan Steurer[4] | Claudia Jafari[5] | Hans Klose[6] | Stefan Kluge[1] | Marcel Simon[6] | Marlene Fischer[1]

- Compare Galactomannan (GM) testing by Enzyme Immunoassay (EIA), GM Lateral Flow Assay (LFA), and PCR between directed BAL and non-directed BL
- A prospective, exploratory pilot study included critically ill patients admitted to the ICU with risk factors for IPA or positive Aspergillus assessments.
- The study enrolled 40 patients admitted to the ICU primarily for respiratory failure or infectious diseases.

Mycoses. 2025;68:e70029

- The performance metrics for non-BAL samples similar those for BAL samples.
- At an ODI cut-off of 1.0, the specificity is 0.86 and sensitivity is 0.91.

Sensitivity and specificity of *Aspergillus* galactomannan enzyme-linked immunosorbent assay for upper and lower bronchial tree samples using different cut-off values.

	GM EIA cut-off for BAL			
	0.8 ODI		1.0 ODI	
GM EIA cut-off for BL	Specificity	Sensitivity	Specificity	Sensitivity
0.8 ODI	0.67	0.90	0.86	0.91
1.0 ODI	0.67	0.90	0.86	0.91
1.2 ODI	0.67	0.94	0.86	0.94
2.0 ODI	0.56	0.97	0.71	0.97
> 3.5 ODI	0.56	0.97	0.71	0.97

Note: The sensitivity and specificity of the *Aspergillus* GM EIA for bronchial lavage (BL) and
values in the table represent the proportion of true negative (specificity) and true positive (se
Abbreviations: EIA, enzyme immunoassay; GM, galactomannan; ODI, optical density index

Coefficients of correlation and agreement of *Aspergillus* EIA, LFA, and PCR between the upper and lower bronchial tree.

Data	Pearson (95% CI)	Spearman	ICC	Kappa coefficient (95% CI)
Aspergillus GM EIA				
Original		0.63	0.82	
Log-transformed	0.78 (0.62, 0.88)		0.78	
Aspergillus GM LFA				
Original		0.49	0.29	
Log-transformed	0.50 (0.22, 0.70)		0.47	
Aspergillus PCR				0.75 (0.48, 1.01)

- Aspergillus GM EIA showed a good correlation between BAL and BL samples, with a Pearson correlation coefficient of 0.78 .
- Aspergillus PCR examination showed good agreement with a Cohen's kappa coefficient of 0.75

Mycoses. 2025;68:e70029

WHICH CRITERIA TO USE ?

Clinical Infectious Diseases
MAJOR ARTICLE

Performance of Diagnostic Algorithms in Patients With Invasive Pulmonary Aspergillosis

- Retrospective Multicentre cohort study with 202 patients across 9 centres from 2014 to 2024
- Patients classified using 4 diagnostic criteria: EORTC-MSG, FUNDICU, Asp-ICU, Asp-ICU-BM.
- Of the 202 patients, 78 were classified using EORTC-MSG criteria, 112 within ICU-focused systems, and 12 were unclassifiable
- Study evaluated the predictive performance of these criteria against the clinical cohort and histologically proven cases
- Proven Cases: There were a total of 22 proven cases identified from 36 autopsies
- Probable Cases: 59 patients were classified as probable IPA based on the FUNDICU criteria.

Hatzl, S. et al. (2024). Clinical Infectious Diseases, 79(3), 456-465

Characteristics of ASP ICU and Asp ICU-BM patients :

Asp-ICU - criteria	n (%)
Aspergillus positive lower respiratory specimen	76 (68%)
- *Aspergillus fumigatus*	71 (63%)
- *Aspergillus niger*	3 (2%)
- *Aspergillus terreus*	1 (1%)
- *Aspergillus flavus*	1 (1%)
Clinical criterion (Fever, pleuritic chest pain, pleuritic rub, dyspnea, hemoptysis, worsening respiratory failure)	112 (100%)
Abnormal medical imaging	111 (99%)
Semiquantitative positive culture (+/++) and absence of bacterial growth	63 (56%)
Cytology evidence of Aspergillus	4 (4%)
Classification:	
Putative IPA:	4 (4%)
Aspergillus colonization	13 (12%)
Diagnostic accuracy:	
Percent positive agreement	4%
Percent negative agreement	100%
Overall agreement	4%

Asp-ICU-BM - criteria	n (%)
Aspergillus positive lower respiratory specimen	76 (68%)
- *Aspergillus fumigatus*	71 (63%)
- *Aspergillus niger*	3 (2%)
- *Aspergillus terreus*	1 (1%)
- *Aspergillus flavus*	1 (1%)
Clinical criterion (Fever, pleuritic chest pain, pleuritic rub, dyspnea, hemoptysis, worsening respiratory failure)	112 (100%)
Abnormal medical imaging	111 (99%)
GM: Single serum or plasma: ODI ≥0.5	61 (55%)
GM: BAL fluid: ODI ≥1.0	83 (74%)
Aspergillus PCR (two consecutive PCR´s)	3 (3%)
Classification:	
Probable IPA:	30 (26%)
Aspergillus colonization	42 (38%)
Diagnostic accuracy:	
Percent positive agreement	26%
Percent negative agreement	100%
Overall agreement	26%

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EORTC Criteria	No. (%)
Host factor	
Recent history of neutropenia	30 (38%)
Hematologic malignancy	41 (53%)
Receipt of an allogeneic stem cell transplant	19 (24%)
Receipt of a solid-organ transplant	15 (19%)
Prolonged use of corticosteroids	51 (65%)
Treatment with T-cell immunosuppressants	30 (38%)
Treatment with B-cell immunosuppressants	11 (14%)
Inherited severe immunodeficiency	1 (1%)
Acute graft-vs-host disease grade III or IV	7 (9%)
Clinical features	
Dense, well-circumscribed lesion(s) with or without a halo sign	62 (79%)
Air crescent sign	32 (41%)
Cavity	15 (19%)
Wedge-shaped and segmental or lobar consolidation	27 (35%)
Mycological evidence	
Aspergillus recovered from sputum, BAL, bronchial brush, or aspirate	33 (42%)
Aspergillus fumigatus	30 (39%)
Aspergillus terreus	1 (1%)
Aspergillus calidoustus	1 (1%)
Aspergillus niger	1 (1%)
Galactomannan	
Single serum or plasma: ≥ 1.0	21 (27%)
Single serum or plasma: ≥ 0.5	44 (56%)
BALF: ≥1.0	49 (63%)
Single serum or plasma: ≥0.7 and BALF ≥0.8	2 (3%)
BALF: ≥2 duplicate PCR tests positive	19 (24%)
Classification	
Probable IPA	67 (86%)
Possible IPA	11 (14%)
Diagnostic accuracy	
Percent positive agreement	100%
Percent negative agreement	100%
Overall agreement	100%

- EORTC-MSG achieved 100% agreement in identifying clinical and histologically proven cases.
- FUNDICU showed 53% agreement with clinical cohort; sensitivity = 44%, specificity = 75%.

FUNDICU Criteria	No. (%)
Host factor	
COVID-19	26 (23%)
Influenza	17 (15%)
Solid tumor	4 (4%)
Uncontrolled HIV infection	1 (1%)
Decompensated cirrhosis	5 (5%)
Moderate/severe COPD	10 (9%)
Compatible signs and symptoms	
Fever persisting after at least 3 d of appropriate antibiotic therapy	17 (15%)
Relapse of fever after a period of at least 48 h of defervescence while still on antibiotics and without other apparent causes	15 (14%)
Pleuritic chest pain	8 (7%)
Pleuritic rubbing of the lungs on examination	3 (2%)
Dyspnea	22 (20%)
Hemoptysis	6 (5%)
Worsening respiratory insufficiency despite appropriate antibiotic therapy and ventilatory support	85 (76%)
Clinical evidence	
Presence of tracheobronchial ulceration and/or nodules and/or pseudo-membrane and/or plaque, and/or eschar on bronchoscopy	6 (5%)
Presence of pulmonary infiltrate(s) by chest CT, or presence of cavitation not attributable to other causes	102 (91%)
Mycological evidence	
Positive *Aspergillus* BALF culture	76 (68%)
Aspergillus fumigatus	71 (63%)
Aspergillus niger	3 (2%)
Aspergillus terreus	1 (1%)
Aspergillus flavus	1 (1%)
Galactomannan	
Single serum or plasma: ODI ≥0.5	61 (55%)
BALF: ODI ≥1.0	83 (74%)
Classification	
Probable IPA	53 (47%)
Probable IPA/TBA	3 (2%)
Probable TBA	3 (2%)
Diagnostic accuracy	
Percent positive agreement	53%
Percent negative agreement	100%
Overall agreement	53%

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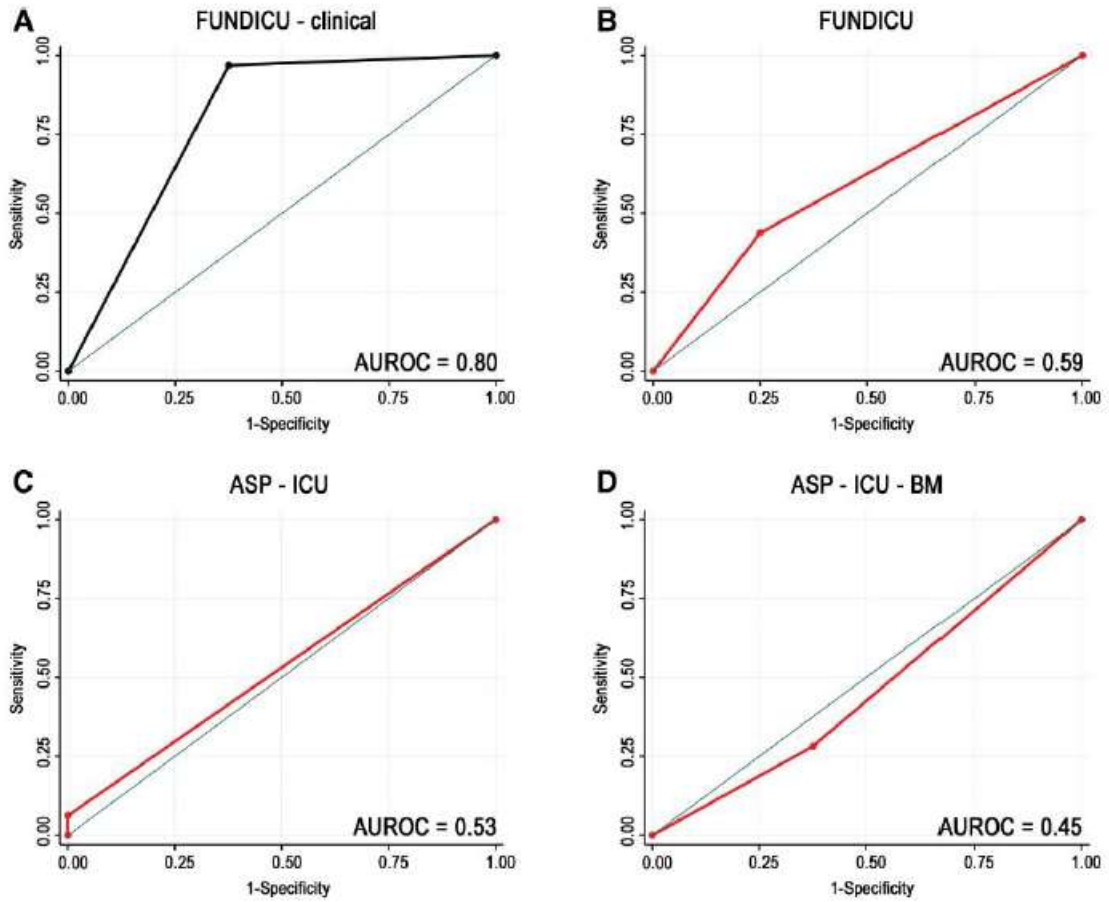

Figure 1. *A–D*, The figure summarizes the diagnostic performance of established algorithms for IPA compared wi
performance was evaluated against histologically proven cases, with AUROC used as the measure of accuracy. Abbr
ASP-ICU-BM, *Aspergillus* in Intensive Care Units with biomarkers; AUROC, area under the receiver operating character
Patients in Intensive Care Unit; IPA, invasive pulmonary aspergillosis.

Table 4. Novel Risk Factors

Risk Factor	No. (%)
Post–complicated cardiac surgery	19 (38%)
Intraoperative massive transfusion (defined as >6 units of packed red blood cells)	19 (100%)
Postoperative pneumothorax	6 (32%)
Postoperative hemothorax	9 (47%)
Postoperative ECMO treatment	10 (53%)
ARDS associated with septic shock (nonpulmonary)	14 (28%)
ARDS (*Streptococcus pneumoniae*)	5 (10%)
OHCA	4 (8%)
Severe pneumonia (severe/moderate ARDS)	5 (10%)
Orthohantavirus	2 (40%)
Legionella pneumophilia	1 (20%)
Staphylococcus aureus	1 (20%)
Mycobacterium tuberculosis/Landouzy sepsis	1 (20%)
Status asthmaticus	1 (2%)
Acute liver failure	1 (2%)
Asbestosis	1 (2%)

- An AUC < 0.5 implies that the test is ineffective for the intended classification
- Adding ARDS and post-cardiac surgery to FUNDICU improved sensitivity to 97% and specificity to 63%.

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A PROSPECTIVE OBSERVATIONAL STUDY ON THE CLINICAL IMPORTANCE OF ASPERGILLUS ISOLATION FROM THE LOWER RESPIRATORY TRACT OF CRITICALLY ILL PATIENTS

FOR THE DEGREE OF

DM (PULMONARY AND CRITICAL CARE MEDICINE)

OF

POSTGRADUATE MEDICAL EDUCATION AND RESEARCH,

CHANDIGARH

BY

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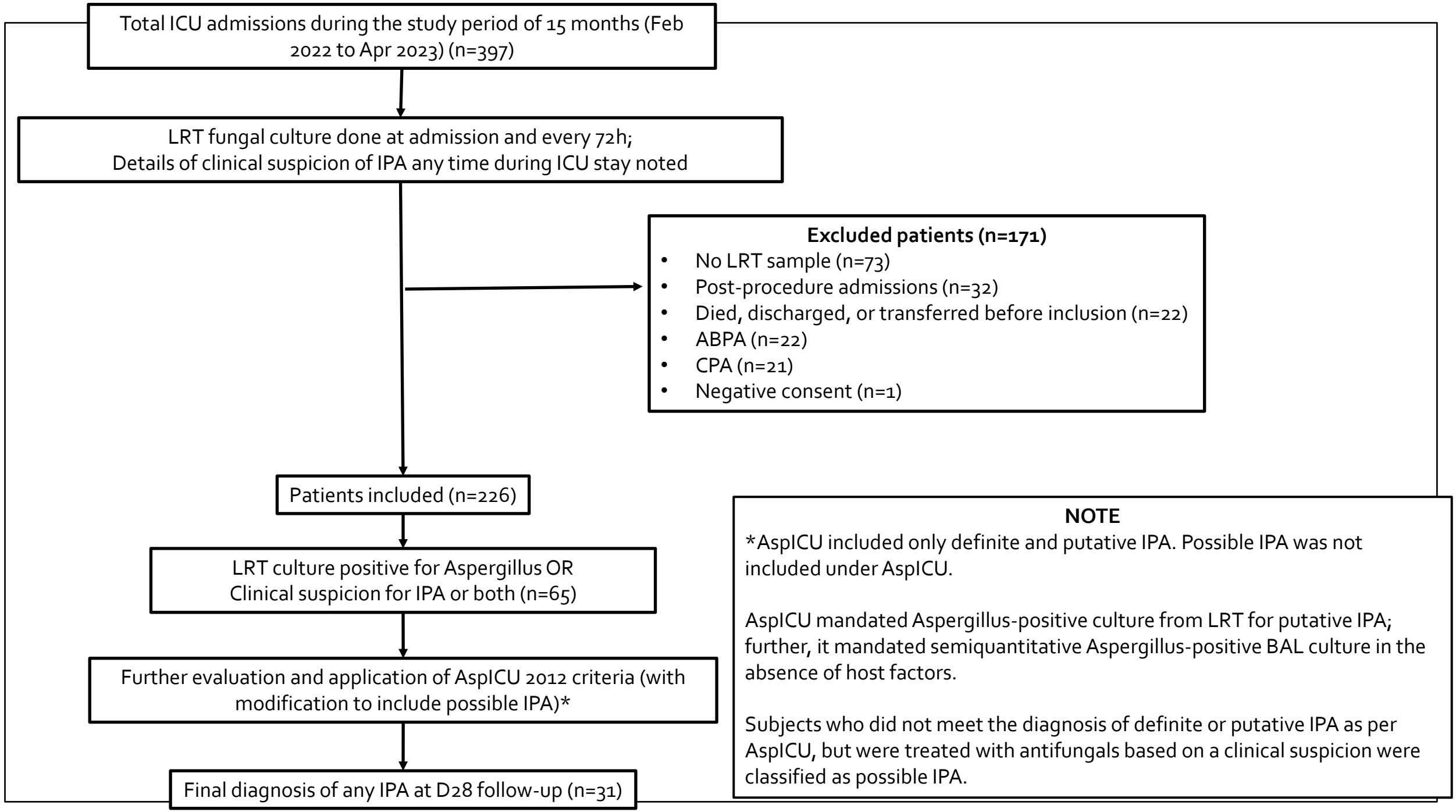
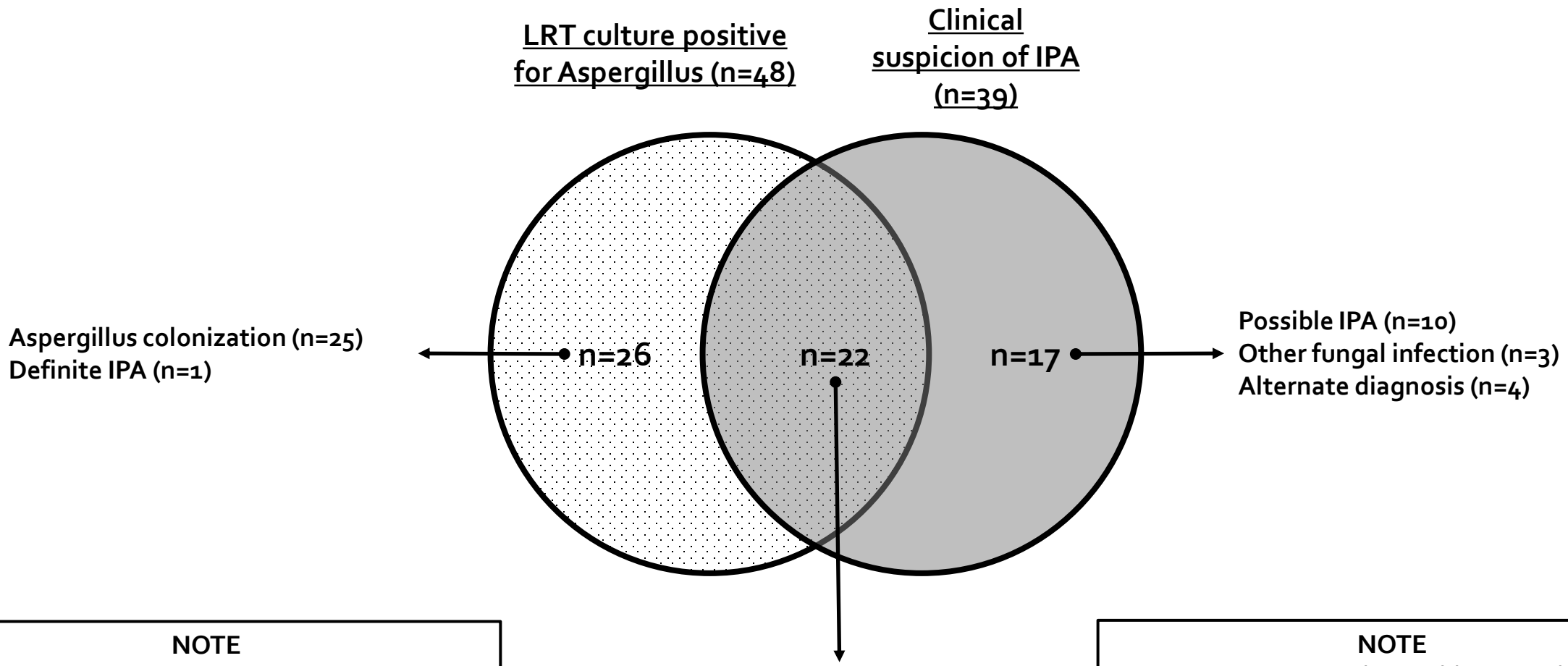

Total ICU admissions during the study period of 15 months (Feb 2022 to Apr 2023) (n=397)
LRT fungal culture done at admission and every 72h;
Details of clinical suspicion of IPA any time during ICU stay noted
Excluded patients (n=171)
• No LRT sample (n=73)
• Post-procedure admissions (n=32)
• Died, discharged, or transferred before inclusion (n=22)
• ABPA (n=22)
• CPA (n=21)
• Negative consent (n=1)
Patients included (n=226)
LRT culture positive for Aspergillus OR
Clinical suspicion for IPA or both (n=65)
Further evaluation and application of AspICU 2012 criteria (with modification to include possible IPA)*
Final diagnosis of any IPA at D28 follow-up (n=31)
NOTE
*AspICU included only definite and putative IPA. Possible IPA was not included under AspICU.
AspICU mandated Aspergillus-positive culture from LRT for putative IPA; further, it mandated semiquantitative Aspergillus-positive BAL culture in the absence of host factors.
Subjects who did not meet the diagnosis of definite or putative IPA as per AspICU, but were treated with antifungals based on a clinical suspicion were classified as possible IPA.

LRT culture positive for Aspergillus or clinical suspicion of IPA (n=65): Final diagnosis at D28 follow-up



NOTE

Among the 65 patients, 17 underwent either post-mortem biopsy or autopsy.

Further, 28d follow-up was performed for all these subjects.

NOTE

Among 19 patients with possible IPA, only 2 survived till D28.

All received antifungals till death or last follow-up at D28.

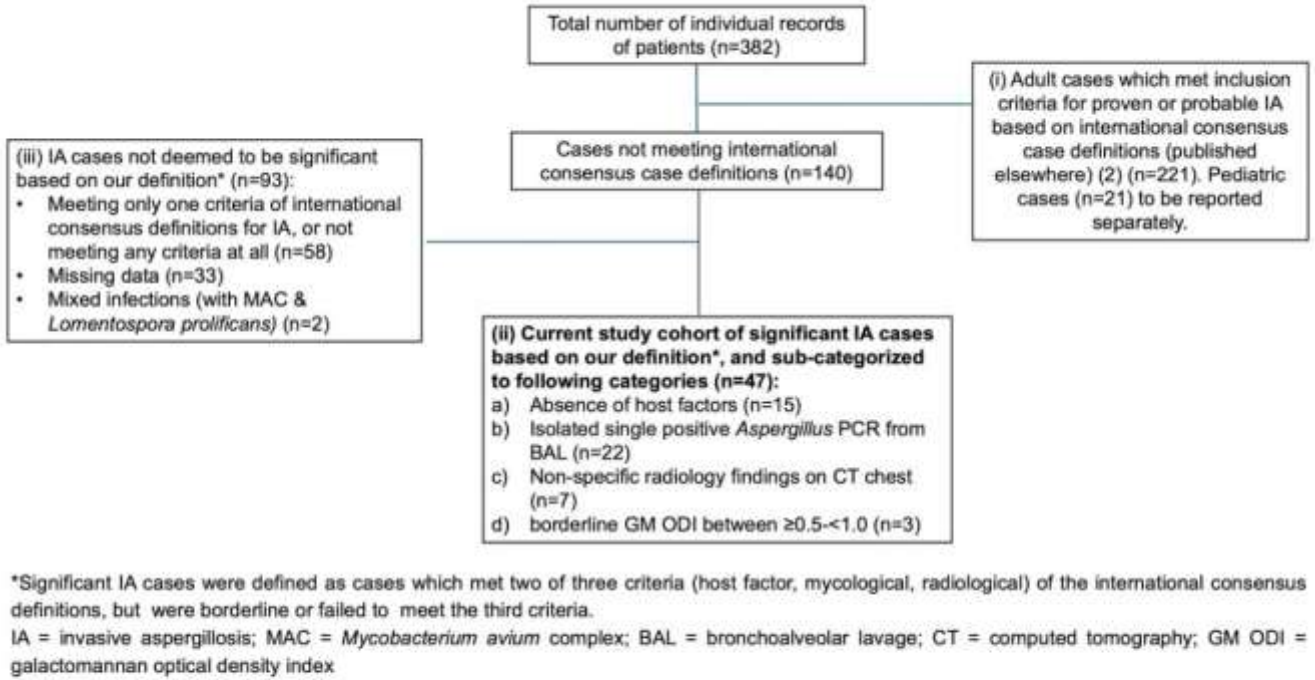
Comparison of criteria in the RICU study

Criteria	Any IPA
Study criteria (AspICU 2012 + Possible IPA)	31/65 (47.7%)
AspICU (Blot 2012)*	12/65 (18.5%)
Modified AspICU (Schauwvlieghe 2018)**	17/65 (26.2%)
Modified AspICU (Loughlin 2020)***	5/65 (7.7%)
EORTC/MSGERC ICU working group definition (Bassetti 2021)****	9/65 (13.8%)

*AspICU (Blot 2012): Aspergillus-positive culture from LRT was entry criterion for putative IPA; further, it mandated semiquantitative Aspergillus-positive BAL culture in the absence of host factors; did not include possible IPA
**Schauwvlieghe 2018: Similar to Blot 2012 criteria except that Aspergillus-positive culture from LRT not mandatory for putative IPA; mycological criteria included BAL and serum GM; used specifically in influenza-associated IPA (hence, other host factors were not needed)
***Loughlin 2020: Similar to Schauwvlieghe 2018; in addition, mandated satisfying of VAP clinical criteria (alteration in temperature, TLC,or ET secretions)
****Bassetti 2021: Host factors leading to immunosuppressed state or other predisposing conditions (HIV infection, decompensated cirrhosis, COPD, bronchiectasis, severe influenza, COVID-19) mandatory for probable IPA; mycological criteria included BAL and serum GM

Open Forum Infectious Diseases
MAJOR ARTICLE

Identifying Gaps in the International Consensus Case Definitions for Invasive Aspergillosis: A Review of Clinical Cases Not Meeting These Definitions



*Significant IA cases were defined as cases which met two of three criteria (host factor, mycological, radiological) of the international consensus definitions, but were borderline or failed to meet the third criteria.
IA = invasive aspergillosis; MAC = *Mycobacterium avium* complex; BAL = bronchoalveolar lavage; CT = computed tomography; GM ODI = galactomannan optical density index

Figure 1. Flow diagram showing disposition of the invasive aspergillosis (IA) cases. *Significant IA cases were defined as cases that met 2 of 3 criteria (host factor, mycologic, radiologic) of the international consensus definitions but were borderline or failed to meet the third criterion. BAL, bronchoalveolar lavage; CT, computed tomography; GM ODI, galactomannan optical density index; MAC, *Mycobacterium avium* complex; PCR, polymerase chain reaction.

Reviews 47 cases not meeting consensus definitions for invasive aspergillosis (IA) to understand why they were excluded from proven/probable IA case definitions.

Clinical, mycologic, and radiologic characteristics were recorded, which were compared with a cohort of 221 proven/probable IA cases

Significant IA - 2 of 3 criteria

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Table 1. Mortality Outcomes and Intensive Care Unit Admissions Between Current Cases (n = 47) and Original Cohort of Proven/Probable Invasive Aspergillosis (n = 221) [2]

	Current Cases Not Meeting International Consensus Definitions (n = 47)	Previous Proven/Probable Cases of Invasive Aspergillosis (n = 221)
Primary outcome		
All-cause 90-d mortality	14 (33)[a]	67 (30)
Secondary outcomes		
All-cause 30-d mortality	8 (17)	40 (18)
All-cause 180-d mortality	18 (45)[b]	78 (35)
Intensive care unit admission	7 (15)	47 (21)
Patients with hematologic malignancy only		
All-cause 90-d mortality	10/26 (43)[c]	42/110 (38)

Similar 90-day mortality rates (33% vs. 30%) despite higher 180-day mortality in the current group (45% vs. 35%).

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Details of Missed cases

1. Age Group: Most patients are elderly, often in their 6os to 8os , .

2. Underlying Conditions:

- Lung cancer

- Chronic obstructive pulmonary disease (COPD)

- Bronchiectasis

- Hematological malignancies (e.g., leukemia)

- HIV/AIDS

- Chronic liver disease

- Previous tuberculosis exposure

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- Showed limitations in current consensus definitions for IA, as mortality in patients not meeting these definitions was similar to those with proven/probable IA.
- Focused on cases that did not meet international IA criteria, which may limit the applicability of its findings to broader populations.
- Modifications to future definitions is needed ??

Conclusion

- Despite the use of multiple diagnostic criteria, diagnosing Invasive Pulmonary Aspergillosis (IPA) remains challenging, especially in ICU patients.
- Overlapping clinical features with other pulmonary conditions contribute to diagnostic complexity.
- A combination of imaging, microbiological, and biomarker-based methods enhances diagnostic accuracy but is not foolproof.
- Continuous advancements and tailored diagnostic approaches are needed for better detection and management.