UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA

COVID-Associated Pulmonary Aspergillosis (CAPA)

Spinello Antinori

Dipartimento di Scienze Biomediche e Cliniche "Luigi Sacco", Milano

Milano 18 Ottobre 2021

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

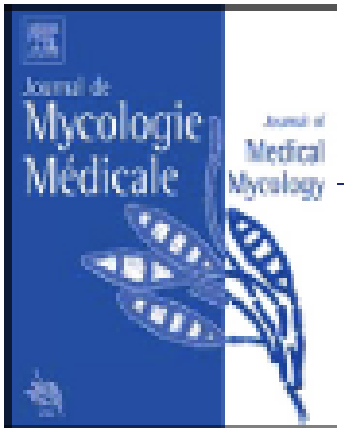
Added value of this study

This study is, to our knowledge, the largest study ever performed on the risk for invasive pulmonary aspergillosis in 432 ICU patients with influenza. It is also the first to evaluate this complication over several consecutive seasons in a large number of ICUs. Furthermore, by comparing non-immunocompromised influenza-positive and influenza-negative patients, we aimed to show that influenza was an independent risk factor for invasive pulmonary aspergillosis. Several conclusions could be drawn. First, the incidence of invasive pulmonary aspergillosis was higher than 10% in each of the seven seasons and was almost equal in patients with influenza A and those with influenza B. Therefore, once a patient with influenza needs intensive care support, the risk for invasive pulmonary aspergillosis does not depend on the influenza season and influenza subtype. Second, the overall incidence of aspergillosis was 19% and was as high as 32% in the subgroup of patients who were also immunocompromised at the time of their influenza infection. The overall mortality in the patients with invasive pulmonary aspergillosis was very substantial at 51%. Finally, we compared invasive pulmonary aspergillosis. We showed that influenza was independently associated with invasive pulmonary aspergillosis (aOR 5·19, 95% CI 2·63–10·26, p<0·0001).

Lancet Respir Med 2018;
6: 782–92

Editorial

Invasive fungal diseases during COVID-19: We should be prepared



Our collective goal is:

- to provide original and still unknown epidemiological data focused on fungal infections during COVID-19; better evaluate the incidence and the dynamic of fungal infection in the course of COVID-19, particularly during the ICU stay;
- to improve the diagnosis, in proposing an efficient syndromic molecular approach for fungal respiratory infection during ARDS that can be shared with all hospitals receiving COVID-19 patients;
- to optimize immediate COVID-19 patient management, with a real-time screening in order to introduce as early as possible a targeted treatment. First-line treatment for aspergillosis, pneumocystosis and mucormycosis are far different and empirical treatments will be avoided as much as possible. Depending on the epidemiological data obtained, preventive strategies such as antifungal chemoprophylaxis and environmental measures could be envisaged with the aim to decrease morbidity and mortality.

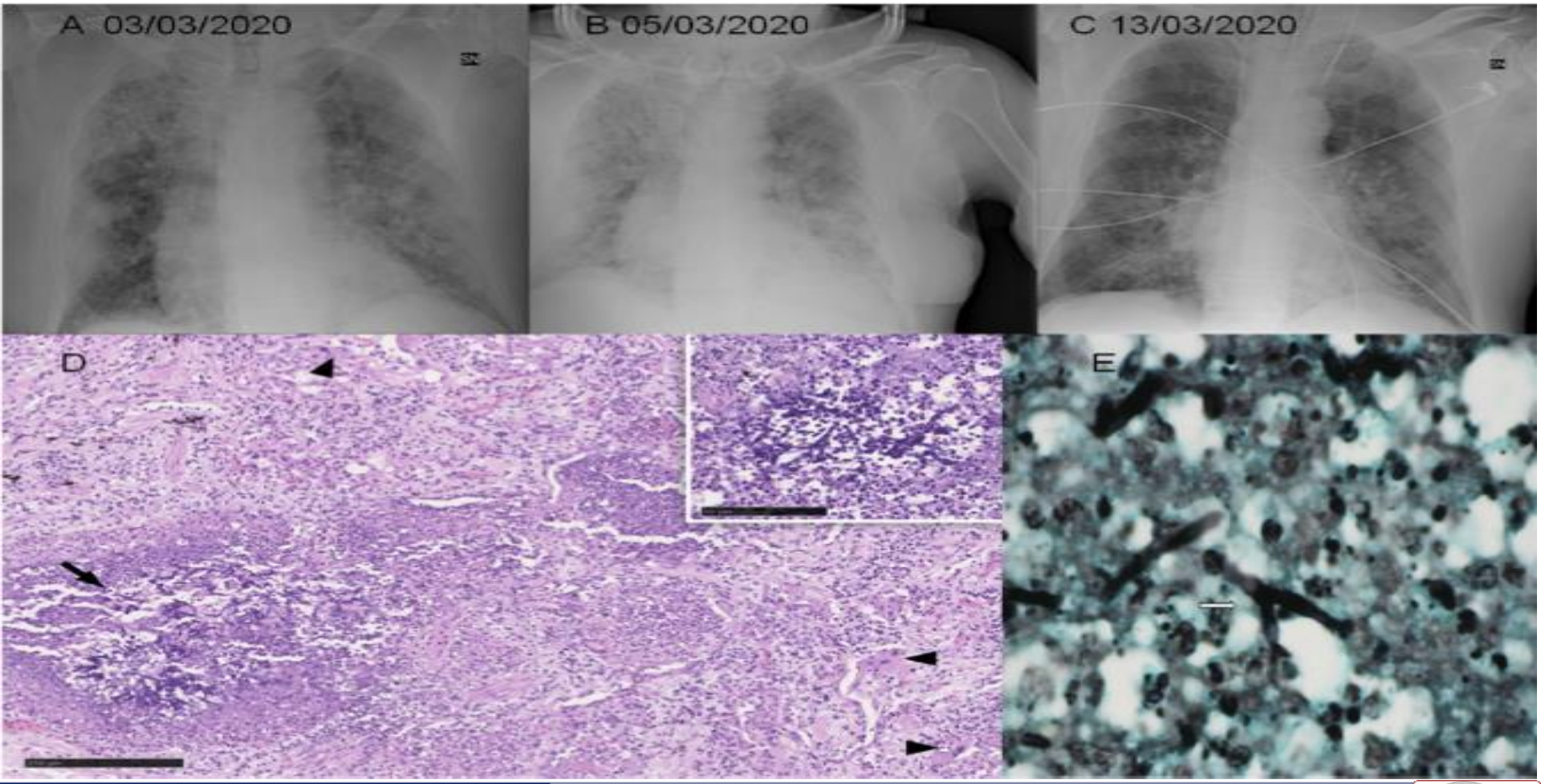
Epub 2020 april 6

Pr J.-P. Gangneux MD, PhDPresident of the Société française de mycologie médicale[a,*], Dr M.-E. Bougnoux MD, PhD[b,c], Dr E. Dannaoui MD, PhD[d], Pr M. Cornet MD, PhD[e], Pr J.R. Zahar MD, PhD[f]

Invasive pulmonary aspergillosis complicating SARS-CoV-2 pneumonia: A diagnostic challenge

Submitted April 2, 2020; accepted May 24,2020

Spinello Antinori[a,b,*], Roberto Rech[c], Laura Galimberti[b], Antonio Castelli[c], Elena Angeli[b], Tommaso Fossali[c], Davide Bernasconi[b], Alice Covizzi[a,b], Cecilia Bonazzetti[a,b], Alessandro Torre[b], Luca Carsana[d], Cristina Tonello[d], Pietro Zerbi[a,d], Manuela Nebuloni[a,d]



Travel Med Infect Dis 2020;38:101752

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

EORTC/MSG

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*

TABLE 1. DIAGNOSTIC CRITERIA FOR INVASIVE PULMONARY ASPERGILLOSIS ACCORDING TO THE EUROPEAN ORGANIZATION FOR TH RESEARCH AND TREATMENT OF CANCER/MYCOSIS STUDY GROUP (3) AND THE CLINICAL ALGORITHM (7)

EORTC/MSG criteria

Proven invasive pulmonary aspergillosis

Microscopic analysis on sterile material: histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or steri biopsy in which hyphae are seen accompanied by evidence of associated tissue damage. Culture on sterile material: recovery of *Aspergillus* by culture of a specimen obtained by lung biopsy

Probable invasive pulmonary aspergillosis (all three criteria must be met)

1. Host factors (one of the following)
   - Recent history of neutropenia (<500 neutrophils/mm^3) for 110 d
   - Receipt of an allogeneic stem cell transplant
   - Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/d of prednisone equivalent for 13 wk
   - Treatment with other recognized T-cell immunosuppressants
   - Inherited severe immunodeficiency
2. Clinical features (one of the following three signs on CT)
   - Dense, well-circumscribed lesion(s) with or without a halo sign
   - Air-crescent sign
   - Cavity
3. Mycological criteria (one of the following)
   - Direct test (cytology, direct microscopy, or culture) on sputum, BAL fluid, bronchial brush indicating presence of fungal elements or culture recovery *Aspergillus* spp.
   - Indirect tests (detection of antigen or cell-wall constituents): galactomannan antigen detected in plasma, serum, or BAL fluid

Possible invasive pulmonary aspergillosis

Presence of host factors and clinical features (cf. probable invasive aspergillosis) but in the absence of or negative mycological findings.

Am J Respir Crit Care Med Vol 186, Iss. 1, pp 56–64, Jul 1, 2012

Target-shaped combined halo and reversed-halo sign, an atypical chest CT finding in COVID-19

Shiva Shaghaghi[a], Mahyar Daskareh[b], Mona Irannejad[a], Mohammadreza Shaghaghi[c], Ihab R. Kamel[c,*]

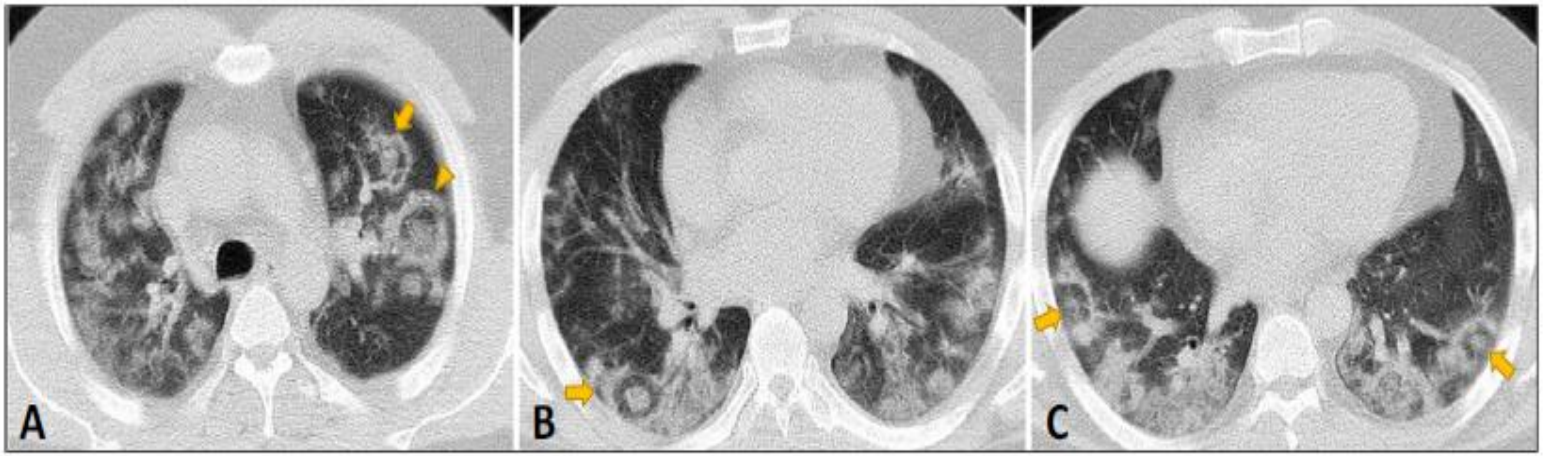


Fig. 1. Baseline chest CT displaying multilobar peripheral consolidations with mixed configuration of 'reversed halo' and 'halo' signs. This appearance was embedded in areas of consolidation. The described patterns were seen in the anterior and apicoposterior segments of the left upper lobe with a maximum size of 33 × 24 mm (arrowhead) (A). Another well visualized peripheral halo consolidation and central round nodule was seen in the posterior segment of the right lower lobe (28 × 18 mm) (B). Two additional areas of peripheral complete halo and central nodular opacity were seen in the lateral segment of the right lower lobe and lateral segment of the left lower lobe, measuring 29 × 21 mm and 25 × 15 mm, respectively (C).

The halo sign as a chest computed tomography finding of COVID-19

O sinal do halo como apresentação tomográfica pulmonar na COVID-19

Lucas de Pádua Gomes de Farias[1,2], Helena Alves Costa Pereira[1], Eduardo Pinheiro Zarattini Anastacio[1], Fernanda Formagio Minenelli[1], Gustavo Borges da Silva Teles[1,2]

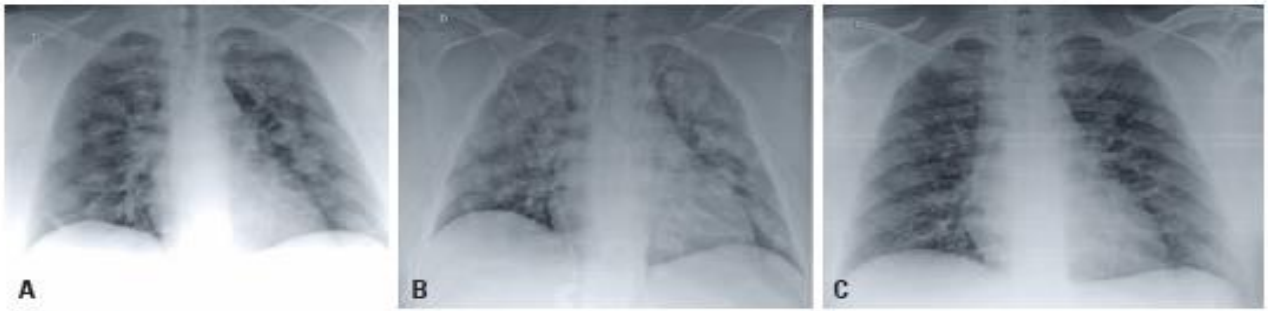
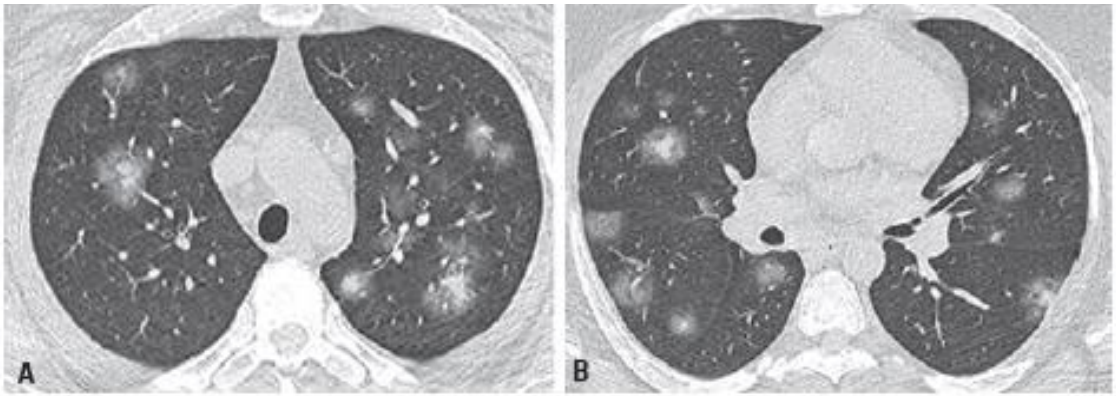


Figure 1. Bedside chest radiography at hospital admission (A), on day 2 (B) and day 10 (C) of hospitalization showed diffuse opacities in both lungs. Many of these opacities are seen to have nodular configuration that were more evident on the 2nd day of hospitalization (B)



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

AspICU

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*

Alternative clinical algorithm

Proven invasive pulmonary aspergillosis
Idem EORTC/MSG criteria

Putative invasive pulmonary aspergillosis (all four criteria must be met)

1. *Aspergillus*-positive lower respiratory tract specimen culture (= entry criterion)
2. Compatible signs and symptoms (one of the following)
   - Fever refractory to at least 3 d of appropriate antibiotic therapy
   - Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause
   - Pleuritic chest pain
   - Pleuritic rub
   - Dyspnea
   - Hemoptysis
   - Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support
3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs
4. Either 4a or 4b
   4a. Host risk factors (one of the following conditions)
      - Neutropenia (absolute neutrophil count $<500/mm^3$) preceding or at the time of ICU admission
      - Underlying hematological or oncological malignancy treated with cytotoxic agents
      - Glucocorticoid treatment (prednisone equivalent, >20 mg/d)
      - Congenital or acquired immunodeficiency
   4b. Semiquantitative *Aspergillus*-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae

Aspergillus respiratory tract colonization

When ≥1 criterion necessary for a diagnosis of putative IPA is not met, the case is classified as *Aspergillus* colonization.

Am J Respir Crit Care Med Vol 186, Iss. 1, pp 56–64, Jul 1, 2012

Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19

with COVID-19. The patients were classified by means of the EORTC-MSG criteria[5] (if immunocompromised) or the influenza-associated IPA criteria[4] combined with serum β-D-glucan and quantitative real-time PCR (qPCR)[7] done in the serum or pulmonary specimens (if non-immunocompromised). Putative IPA was considered if *Aspergillus* spp were identified in BAL culture; or if two of the following conditions were met (ie, presence of *Aspergillus* spp in bronchial aspiration [BA] culture; positive *Aspergillus fumigatus* qPCR in BAL, BA, or serum;[8] galactomannan index >0·8 in BAL;[5] galactomannan index >0·5 in serum; and β-D-glucan >80 pg/mL in serum).

27 successive mechanically ventilated patients with COVID-19 (18 male and nine female, median age 63 years [IQR 56-71]) were included. Specimens (20 BALs and seven BAs) were obtained on day 3 [IQR 1–6] post-intubation. Probable IPAs were diagnosed in one patient (4%) and putative IPAs were diagnosed in eight patients (30%; table). Putative IPA diagnosis relied on *Aspergillus* spp identification in BAL culture (n=2) and validation of 2 or more mycological criteria (n=6).

UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA

*Alexandre Alanio, Sarah Dellière, Sofiane Fodil, Stéphane Bretagne, Bruno Mégarbane
alexandre.alanio@pasteur.fr

	Putative invasive pulmonary aspergillosis patients (sex, age)								Probable IPA patient (sex, age)
	Patient 1 (male, 53 years)	Patient 2 (female, 59 years)	Patient3 (female, 69 years)	Patient 4 (female, 63 years)	Patient 5 (male, 43 years)	Patient 6 (male, 79 years)	Patient 7 (male, 77 years)	Patient 8 (female, 75 years)	Patient 9 (male, 47 years)
Risk factors of severe COVID-19	Hypertension, obesity, ischaemic heart disease	Hypertension, diabetes, obesity	Hypertension, obesity	Hypertension, diabetes, ischaemic heart disease	Asthma	Hypertension	Hypertension, asthma	Hypertension, diabetes	None
EORTC risk factors	None	None	None	None	Steroids	None	None	None	Myeloma, steroids
APACHE II score	26	16	11	20	8	16	25	21	10
Thoracic CT-scan/x-ray*	Typical COVID-19	Typical COVID-19	Typical COVID-19	Typical COVID-19	Typical COVID-19	Typical COVID-19, segmental lung atelectasis	Typical COVID-19, emphysema	Typical COVID-19	Typical COVID-19 + one peripheral nodule
Anti-COVID-19 therapies	LPV–RTV	LPV–RTV, AZI	LPV–RTV	LPV–RTV	AZI	LPV–RTV, HCQ, AZI	LPV–RTV, HCQ, AZI	LPV–RTV, AZI	No
Steroids to treat pneumonia†	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No
Renal replacement therapy	Yes	No	No	Yes	No	No	Yes	No	No
Vasopressor	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Pulmonary specimen‡	BAL	BAL	BA	BAL	BAL	BAL	BAL	BAL	BA
Invasive pulmonary aspergillosis diagnosis									
BAL culture§	–	+	+	–	+	+	+	+	+
BAL/BA qPCR¶	–	–	23·9	–	–	34·5	29·0	31·7	–
BAL galactomannan index	0·89	0·03	ND	0·15	0·12	0·05	3·91	0·36	ND
Serum qPCR¶	–	–	–	ND	–	–	–	–	–
β-D-glucan, pg/mL	523	ND	7·8	105	7	23	135	450	14
Serum galactomannan index	0·13	0·04	0·03	0·51	0·04	0·02	0·37	0·37	0·09
Number of mycological criteria	2	1	2	2	1	2	3	3	1
Antifungal therapy	None	None	None	None	None	None	VRC	CSP	None
Outcome	Alive	Alive	Alive	Death (day 0)	Alive	Alive	Death (day 18)	Death (day 11)	Death day 3)

EORTC=European Organization for Research and Treatment of Cancer. APACHE= Acute Physiology and Chronic Health Enquiry. LPV–RTV=lopnavir–ritonavir combination. AZI=azithromycin.

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

Paul E. Verweij[1,2*], Bart J. A. Rijnders[3], Roger J. M. Brüggemann[2,4], Elie Azoulay[5], Matteo Bassetti[6,7], Stijn Blot[8,9], Thierry Calandra[10], Cornelius J. Clancy[11,12], Oliver A. Cornely[13,14,15], Tom Chiller[16], Pieter Depuydt[17], Daniele Roberto Giacobbe[6,18], Nico A. F. Janssen[2,19], Bart-Jan Kullberg[2,19], Katrien Lagrou[20,21], Cornelia Lass-Flörl[22], Russell E. Lewis[23], Peter Wei-Lun Liu[24,25], Olivier Lortholary[26,27], Johan Maertens[20,28], Ignacio Martin-Loeches[29,30], M. Hong Nguyen[11,12], Thomas F. Patterson[31,32], Thomas R. Rogers[33], Jeroen A. Schouten[34,35], Isabel Spriet[36], Lore Vanderbeke[20,37], Joost Wauters[37] and Frank L. van de Veerdonk[2,19]

Abstract

Purpose: Invasive pulmonary aspergillosis is increasingly reported in patients with influenza admitted to the intensive care unit (ICU). Classification of patients with influenza-associated pulmonary aspergillosis (IAPA) using the current definitions for invasive fungal diseases has proven difficult, and our aim was to develop case definitions for IAPA that can facilitate clinical studies.

Methods: A group of 29 international experts reviewed current insights into the epidemiology, diagnosis and management of IAPA and proposed a case definition of IAPA through a process of informal consensus.

Results: Since IAPA may develop in a wide range of hosts, an entry criterion was proposed and not host factors. The entry criterion was defined as a patient requiring ICU admission for respiratory distress with a positive influenza test temporally related to ICU admission. In addition, proven IAPA required histological evidence of invasive septate hyphae and mycological evidence for *Aspergillus*. Probable IAPA required the detection of galactomannan or positive *Aspergillus* culture in bronchoalveolar lavage (BAL) or serum with pulmonary infiltrates or a positive culture in upper respiratory samples with bronchoscopic evidence for tracheobronchitis or cavitating pulmonary infiltrates of recent onset. The IAPA case definitions may be useful to classify patients with COVID-19-associated pulmonary aspergillosis (CAPA), while awaiting further studies that provide more insight into the interaction between *Aspergillus* and the SARS-CoV-2-infected lung.

Intensive Care Med
https://doi.org/10.1007/s00134-020-06091-6

Epub June 2020

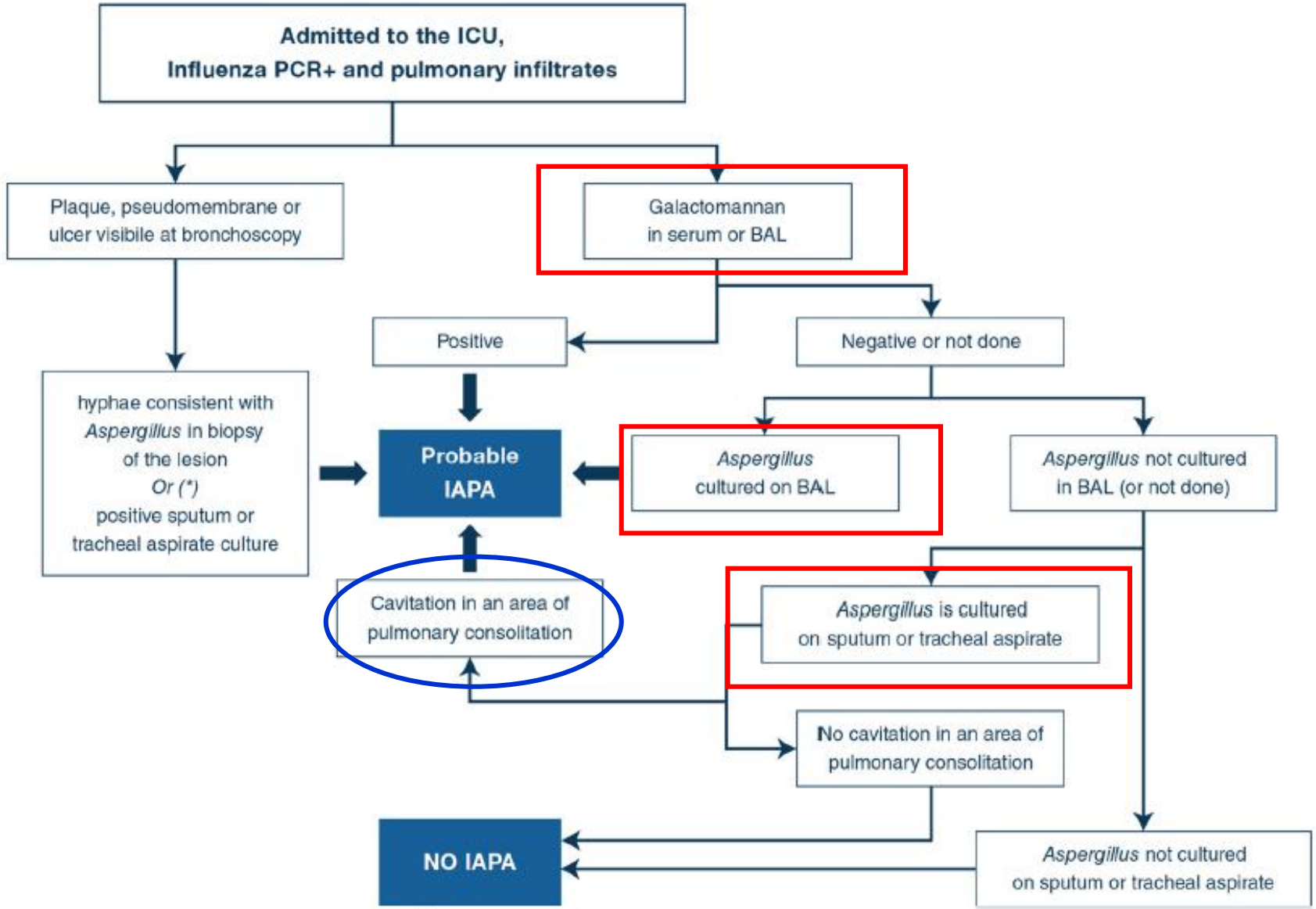


Fig. 1 Flowchart of probable IAPA classification. (*)If hyphae consistent with *Aspergillus* are documented in a biopsy of an airway lesion AND *Aspergillus* is grown from sputum or a tracheal aspirate, the case fulfills the definition of proven IAPA

Verveji PE et al. Intensive Care Med 2020

Is the COVID-19 Pandemic a Good Time to Include *Aspergillus* Molecular Detection to Categorize Aspergillosis in ICU Patients? A Monocentric Experience

Journal of Fungi

July 2020

Jean-Pierre Gangneux [1,2,*], Florian Reizine [3], Hélène Guegan [1,2], Kieran Pinceaux [3], Pierre Le Balch [3], Emilie Prat [1], Romain Pelletier [1], Sorya Belaz [1], Mathieu Le Souhaitier [3], Yves Le Tulzo [3], Philippe Seguin [4], Mathieu Lederlin [5], Jean-Marc Tadié [3] and Florence Robert-Gangneux [1,2]

A cohort of 45 COVID-19 intubated and mechanically ventilated patients for ARDS was followed. Patients benefited from a systematic screening for *Aspergillus*. Overall, 211 respiratory samples (culture and PCR) and 32 serum samples (GM detection and *Aspergillus* PCR) were collected. The mean number of respiratory samples until patient discharge from ICU was 3.8 (median = 3).

We categorized these 45 patients according to the AspICU algorithm and propose two alternative classification methods presented in Table 1: the AspICU algorithm associated to PCR results in respiratory and serum samples, and a modified AspICU proposal. Thirty patients did not present any biological criteria of aspergillosis with any of the algorithms. According to the AspICU classification incorporating PCR detection, 15 were classified as having putative aspergillosis because they met all criteria reported by Blot et al., i.e., compatible clinical signs, abnormal thoracic medical imaging on CT scan and positive screening for *Aspergillus* on respiratory samples. However, in this particular context of COVID-19 with all ARDS patients presenting compatible clinical signs and abnormal chest CT imaging in all likelihood lacking specificity, we decided to use a modified AspICU

Table 2. Classification of 45 COVID-19 patients with ARDS according to AspICU and to modified AspICU algorithms.

Classification	AspICU According to Blot et al., 2012 [3]	AspICU Algorithm Incorporating PCR	Modified AspICU Algorithm Incorporating PCR, Serology and Angioinvasion Biomarkers
No infection	36	30	30
Colonization	0	0	8
Putative IA	9	15	4
Probable IA	-	-	3
Proven IA	0	0	0

Table 1. Diagnostic criteria of the AspICU clinical algorithm according to Blot et al., 2012, and proposal of a modified AspICU algorithm.

Classification	AspICU According to Blot et al., 2012 [3]	AspICU Algorithm Incorporating PCR	Modified AspICU Algorithm Incorporating PCR, Serology and Angioinvasion Biomarkers
Definition of colonization	*Aspergillus*-positive culture endotracheal aspirate alone	*Aspergillus*-positive culture/PCR endotracheal aspirate alone	*Aspergillus*-positive culture/PCR endotracheal aspirate in one sample, not confirmed on a second sample or using blood biomarker
Definition of putative IA	>1 criterion among: 1. *Aspergillus*-positive culture endotracheal aspirate 2. Compatible clinical signs 3. Abnormal thoracic medical imaging on CT scan or X-ray 4a. Host risk factors Or 4b. Semiquantitative *Aspergillus*-positive culture of BAL fluid + positive direct microscopy	>1 criterion among: 1. *Aspergillus*-positive culture/PCR endotracheal aspirate 2. Compatible clinical signs 3. Abnormal thoracic medical imaging on CT scan or X-ray 4a. Host risk factors Or 4b. Semiquantitative *Aspergillus*-positive culture/PCR of BAL fluid + positive direct microscopy	>1 criterion among: 1. *Aspergillus*-positive culture/PCR endotracheal aspirate in repeated samples with negative anti-*Aspergillus* antibody testing 2. Compatible clinical signs 3. Abnormal thoracic medical imaging on CT scan or X-ray 4a. Host risk factors Or 4b. Semiquantitative *Aspergillus*-positive culture/PCR of BAL fluid + positive direct microscopy
Definition of probable IA	-	-	Putative IA + one positive blood biomarker (GM and/or PCR)
Definition of proven IA	Positive histopathology	Positive histopathology	Positive histopathology

Table 6. Mycological results and classification of 45 COVID-19 patients with ARDS.

Patient	Respiratory Samples		Serum Samples		IA Classification According to		
	Aspergillus positive culture (nb samples)	Positive 28S PCR (nb samples)	GM index > 0.5 (nb samples)	Positive 28S PCR (nb samples)	AspICU (Blot et al., 2012)	AspICU + PCR	Modified AspICU
1	5	5	2	2	putative	putative	probable
2	2	2	1	1	putative	putative	probable
3	0	3	0	1	no infection	putative	probable
4	4	6	0	0	putative	putative	putative
5	4	4	0	0	putative	putative	putative
6	2	5	0	0	putative	putative	putative
7	1	5	0	0	putative	putative	putative
8	1	1	0	0	putative	putative	colonization
9	1	0	1	0	putative	putative	colonization
10	1 *	0	0	0	putative	putative	colonization
11	0	1	0	0	no infection	putative	colonization
12	0	1	0	0	no infection	putative	colonization
13	0	1	0	0	no infection	putative	colonization
14	0	1	0	0	no infection	putative	colonization
15	0	1	0	0	no infection	putative	colonization
16–45	0	0	0	0	no infection	no infection	no infection
Total					9 putative (22%) 36 no infection	15 putative (33%) 30 no infection	3 probable (7%) 4 putative (9%) 8 colonizations (18%) 30 no infection

IA. Invasive aspergillosis, 1 * *Aspergillus tubingensis* (*Nigri* section).

COVID-19–Associated Pulmonary Aspergillosis, March–August 2020

Jon Salmanton-García, Rosanne Sprute, Jannik Stemler, Michele Bartoletti, Damien Dupont, Maricela Valerio, Carolina Garcia-Vidal, Iker Falces-Romero, Marina Machado, Sofía de la Villa, Maria Schroeder, Irma Hoyo, Frank Hanses, Kennio Ferreira-Paim, Daniele Roberto Giacobbe, Jacques F. Meis, Jean-Pierre Gangneux, Azucena Rodríguez-Guardado, Spinello Antinori, Ertan Sal, Xhorxha Malaj, Danila Seidel, Oliver A. Cornely,[1] Philipp Koehler,[1] The FungiScope European Confederation of Medical Mycology/The International Society for Human and Animal Mycology Working Group[2]

Table 1. Pathogens of 186 patients with coronavirus disease–associated pulmonary aspergillosis, March–August 2020*

Characteristic	No. (%)
Pathogens†	
Aspergillus fumigatus	122 (65.6)
A. niger	13 (7.0)
A. flavus	10 (5.4)
A. terreus	6 (3.2)
A. calidoustus	1 (0.5)
A. lentulus	1 (0.5)
A. nidulans	1 (0.5)
A. penicillioides	1 (0.5)
A. versicolor	1 (0.5)
A. tubingensis	1 (0.5)
Aspergillus spp. (culture)‡	1 (0.5)
Aspergillus spp. (serologic techniques)	34 (18.3)
Other pathogens§	40 (21.5)
Case definition	
EORTC/MSG criteria (*21*)	
Proven	7 (3.8)
Probable	10 (5.4)
Nonclassifiable	169 (90.9)
AspICU algorithm (*23*)¶	
Proven	7 (3.8)
Putative	142 (76.3)
Colonization	34 (18.3)
Nonclassifiable	3 (1.6)
Consensus definition (reference 57 in Appendix)	
Proven	7 (3.8)
Probable	82 (44.1)
Possible	19 (10.2)
Nonclassifiable¶#	78 (41.9)
Mycologic evidence	
Culture**	152 (81.7)
Microscopy††	3 (1.6)
Histologic techniques‡‡	7 (3.8)
PCR§§	43 (23.1)
Galactomannan test¶¶	113 (60.8)

tool that produced a positive result. Galactomannan (GM) levels were positive (i.e., optical density index ≥1.0) in samples from 113 (60.8%) patients, including BAL samples from 63 (33.9%) patients, serum or plasma from 29 (15.6%), and NBL from 22 (11.8%).

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

Table 4 All-cause mortality in COVID-19 patients with CAPA compared with controls

Country	Case definition	# of CAPA patients	Mortality in CAPA	Mortality in controls	References
France	EORTC/MSGERC (if immunocompromised) [7] and IAPA [5]	9	44%	39% ($p=0.99$)	[15]
France[a]	Modified IAPA [8, 9] and EORTC/MSGERC [7]	21	71.4%	36.8% ($p<0.01$)	[35]
Italy	IAPA [5]	30	44% (day 30)	19% (day 30) ($p=0.002$)[b]	[19]
	AspICU [8]	19	74%	26% ($p<0.001$)	
United Kingdom		19	58% (day 77?)	38%	[20]
Netherlands	2020 ECMM/ISHAM [10]	19	63.6%	23.1% ($p=0.013$)	[28]
USA	2020 ECMM/ISHAM [10]	20	50%	41.5%	[29]

[a] Includes cohort of Alanio et al. [15]

[b] Diagnosis of CAPA was associated with 30-day mortality from ICU admission (OR 3.53; 95% CI 1.29–9.67; $p=0.014$), even after adjustment for age (OR 0.99; 95% CI 0.94–1.06; $p=0.99$), need for renal replacement therapy (OR 3.02; 95% CI 1.11–8.19; $p=0.015$), and SOFA score at ICU admission (OR 1.38; 95% CI 1.07–1.73; $p=0.004$) with a logistic regression model [19]

Table 3 Reported characteristics of cohort studies of CAPA in ICU patients that utilized bronchoscopy

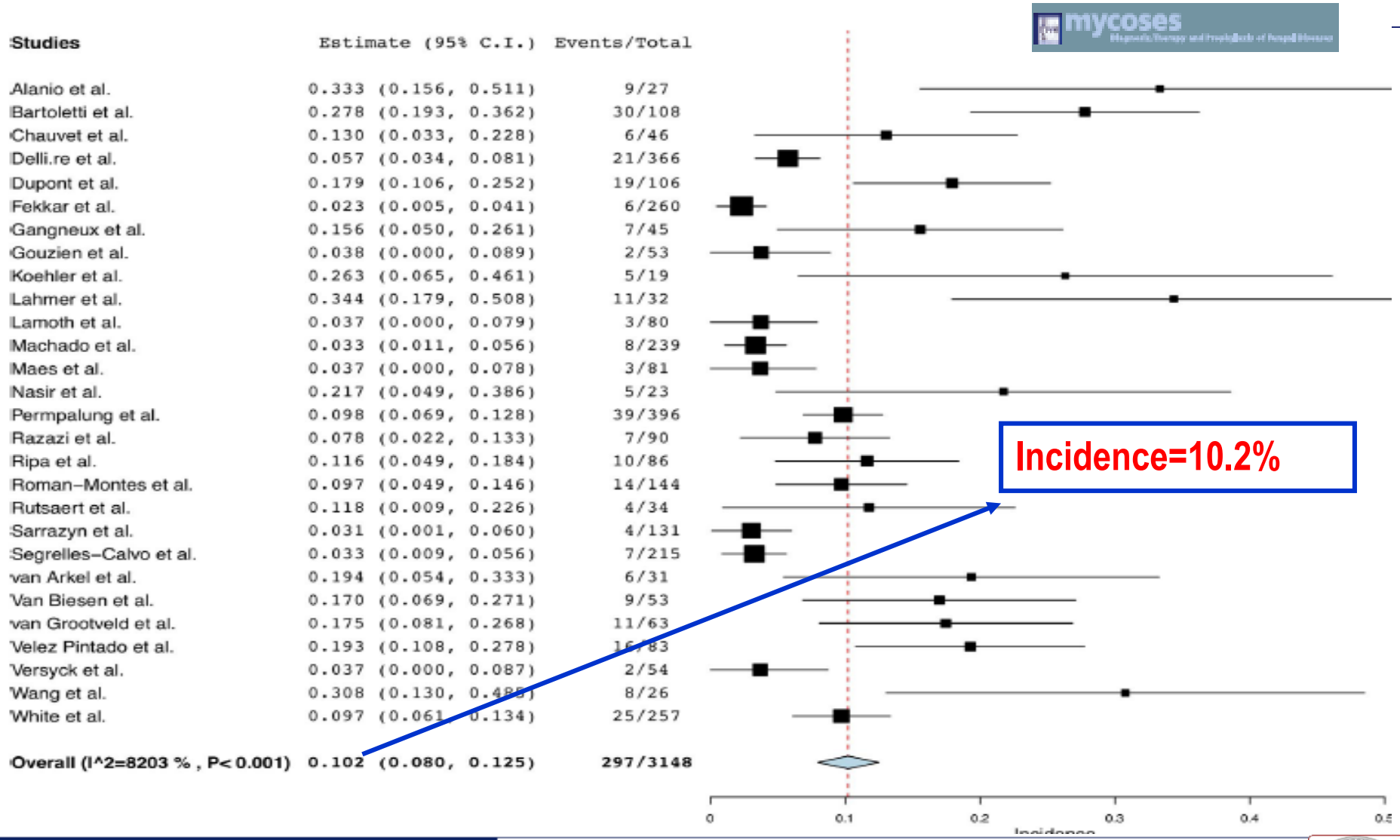
Country	Case definition	CAPA prevalence	Time to first *Asp.* positive sample after ICU admission in days (range)[a]	Ventilated	Proven/probable/putative	References
France	EORTC/MSGERC (if immunocompromised) [7] and IAPA [5]	9/27 (33%)	Not specified	27/27	0/1/8	[15]
France[b]	Modified IAPA [3] and EORTC/MSGERC [7]	21/366 (5.7%)	6 (1 -15)	246/366	0/21/0	[33]
Germany	Modified *AspICU* [8, 9]	5/19 (26%)	Not specified	5/5	0/–/5	[16]
Netherlands	Modified IAPA [3]	6/31 (19%)	10 (3 – 28)	6/6	0/3/3	[17]
Belgium	*AspICU* [8]	6/34 (21%)	8 (2 – 16)	6/6	4/–/2	[18]
Italy	Modified IAPA [3]	30/108 (28%)	4 (2 – 8) days[c] (study used screening protocol)	30/30	0/30/–	[19]
	AspICU [8]	19/108 (18%)	8 (0 – 35)[d]	19/19	0/–/19	
UK	*AspICU* [8]	8/135 (6%)		7/8	0/–/8	[20]
	IAPA [5]	20/135 (15%)		15/20	0/–/20	
	Own definition	19/135 (14%)		14/19	0/–/19	
Belgium	Modified *AspICU* [8, 9]	4/131 (3%)	4	4/4	0/–/4	[21]
Switzerland	Modified IAPA [3]	3/80 (4%)[¥]	6 (3–8)	3/3	0/1/2	[22]
France	Modified *AspICU* [8, 9]	19/106 (18%)	11 (2–23)	18/19	0/–/19	[23]
France	EORTC/MSGERC (if immunocompromised) [7] and IAPA [5]	7/145 (5%)	10 (median)	27/27	0/0/7	[24]
Ireland	Not stated	0/55	–	Not stated	0/0/0	[36]
Netherlands	2020 ECMM/ISHAM consensus definitions [10]	7/33 (21%)	Not specified	Not specified	0/7/–	[27]
Netherlands	2020 ECMM/ISHAM consensus definitions [10]	11/63 (17%)	21 (13–27)	10/11	0/11/–	[28]
USA	2020 ECMM/ISHAM consensus definitions [10]	20/396 (5%)	13 (8.5–28)	20/20	0/20/19[e]	[29]

[a] Time to positivity: Antinori et al. culture sample taken at day 4 positive [37]. Ghelfenstein-Ferreira et al. culture positive with *A. fumigatus* of sample taken at day 6 after ICU admission [38]. Meijer et al. recovered *A. fumigatus* from a tracheal aspirate culture at ICU admission [39]. Mitaka et al. found that the 6 patients were mechanically ventilated for a mean of 6.8 days (range 1–14 days) before *Aspergillus* isolation [25]. The two patients described by Helleberg had growth of *A. fumigatus* in respiratory samples 1 and 5 days after starting mechanical ventilation [40]

[b] Includes cohort of Alanio et al. [15]

[c] 80 mechanical ventilated patients of a total of 118 patients admitted to the ICU

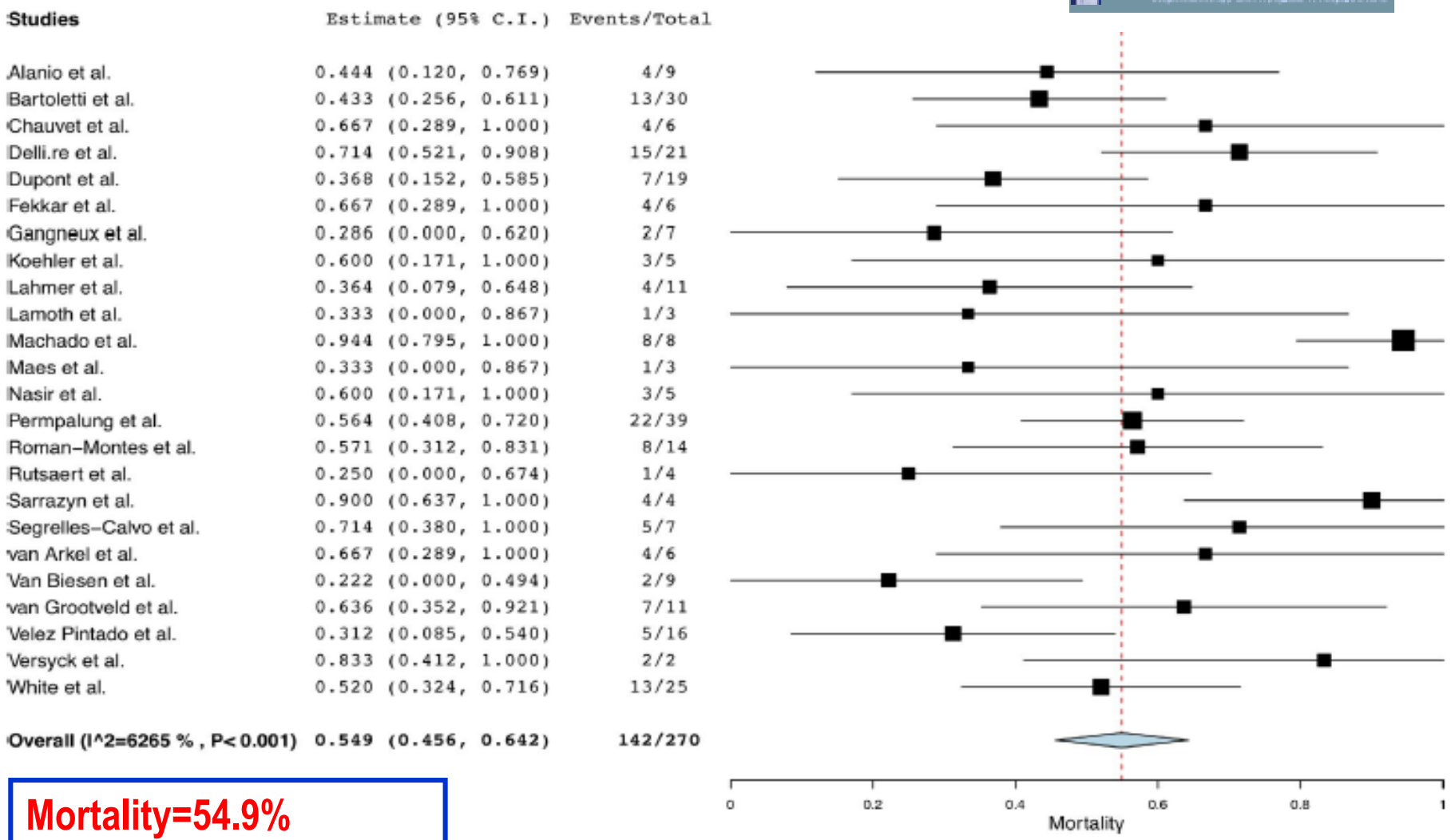
Incidence and mortality of COVID-19-associated pulmonary aspergillosis: A systematic review and meta-analysis



Mitaka H et al. 2021;00:1-9

Incidence and mortality of COVID-19-associated pulmonary aspergillosis: A systematic review and meta-analysis

mycoses



Mortality=54.9%

Mitaka H et al. 2021;00:1-9

Late histopathologic characteristics of critically ill COVID-19 patients: Different phenotypes without evidence of invasive aspergillosis, a case series

Post-mortem needle core lung biopsies

Antine W. Flikweert [a,*], Marco J.J.H. Grootenboers [a], David C.Y. Yick [b], Arthur W.F. du Mée [c], Nardo J.M. van der Meer [d], Thijs C.D. Rettig [d], Merijn K.M. Kant [a,d]

Patient characteristics and clinical course.

Case	Sex, age (years)	Medical history	Total hospital days	Total ventilated days	Berlin classification of ARDS	Compliance phenotype	PE	BAL fluid GM and culture (days post hospital admission)	CAPA	Chloroquine	Prednisolone use during hospital admission	Duration of prednisolone treatment
1	M, 77	None	12	10	Severe	Low	Yes	GM negative	No	Yes	No	
2	F, 73	None	20	16	Severe	High	Yes	GM index 4.4 (day 19) *Aspergillus fumigatus*	Probable	No	Yes	8 days
3	F, 58	None	30	26	Severe	Low	Yes	GM index 3.4 (day 20)	Probable	Yes	Yes	5 days
4	M, 68	None	21	21	Moderate	Low	Yes	GM index 5.7 (day 1) *Aspergillus fumigatus* *Enterococcus faecium*	Probable	Yes	No	
5	M, 78	HT, CKI	22	21	Moderate	Low	No	GM index 4.3 (day 20) *Enterococcus faecium*	Probable	Yes	Yes	2 days
6	M, 83	HT, DM	13	9	Moderate	Low	No	GM index 1.7 (day 11)	Probable	Yes	No	
7	M, 74	None	36	36	Severe	Low	Yes	GM index 4.4 (day 24) *Enterococcus faecalis*	Probable	Yes	Yes	4 days

ARDS acute respiratory distress syndrome; BAL broncho-alveolar lavage; CAPA, COVID-19 associated pulmonary aspergillosis; CKI, chronic kidney injury; DM, diabetes mellitus; GM, galactomannan; HT, hypertension; PE pulmonary embolism.

Invasive mould disease in fatal COVID-19: a systematic review of autopsies

Brittany E Kula, Cornelius J Clancy, M Hong Nguyen, Ilan S Schwartz

A total of 677 decedents were reported across the 50 studies (table 1).[22–71] Information on the use of fungal stain procedures was available for 42 studies comprising 617 decedents (91%). Fungal stains were routinely used for examination of lung tissue in 17 studies (table 1) comprising 257 decedents (38%); for 25 studies, comprising 380 decedents (56%), fungal stains were added if there were findings suggestive of bronchopneumonia on haematoxylin and eosin stain. Studies were included from 15 countries, most commonly from the USA (including 199 decedents), Italy (n=146), and Germany (n=84; figure 2). Most autopsies were done on decedents who were admitted to hospital (n=665 [98%]) with very few from the community (n=12 [2%]). Standard autopsy was the most commonly used technique (36 [72%] studies). Minimally invasive autopsy was used in ten (20%) studies and a combination of standard and minimally invasive autopsies was used in five (10%) studies (table 1). Invasive

	Invasive mould disease (n=10 [2%])	No invasive mould disease (n=433 [98%])
Median age, years (IQR)	60 (40–75·5)	70 (57–79)*
Male	9/9 (100%)	260/393 (66%)
Pre-existing lung disease	1/9 (11%)	94/392 (24%)
Immunocompromised	1/9 (11%)	26/407 (6%)
Median duration from symptom onset to death, days (IQR)	9 (6·8–22·5)†	14 (9–26)†
Median hospital length of stay, days (IQR)	14·0 (5·5–26·0)‡	10·0 (5·0–22·5)§
Ventilated	6/10 (60%)	172/339 (51%)
Median ventilation time, days (IQR)	7·0 (6·5–15·5)¶	9·0 (5·0–20·0)‖
Host-directed therapies for COVID-19	1/9 (11%)	59 (14%)

Data missing for *60 decedents, †3 decedents, ‡5 decedents, §112 decedents, ¶1 decedent, and ‖37 decedents.

Table 3: Individual-level data for decedents with and without autopsy-proven invasive mould disease

Autopsy proven mold disease in Covid-19= 2%

Lancet Microbe 2021; 2:e405-14

Comparing the clinical characteristics and outcomes of COVID-19-associate pulmonary aspergillosis (CAPA): a systematic review and meta-analysis

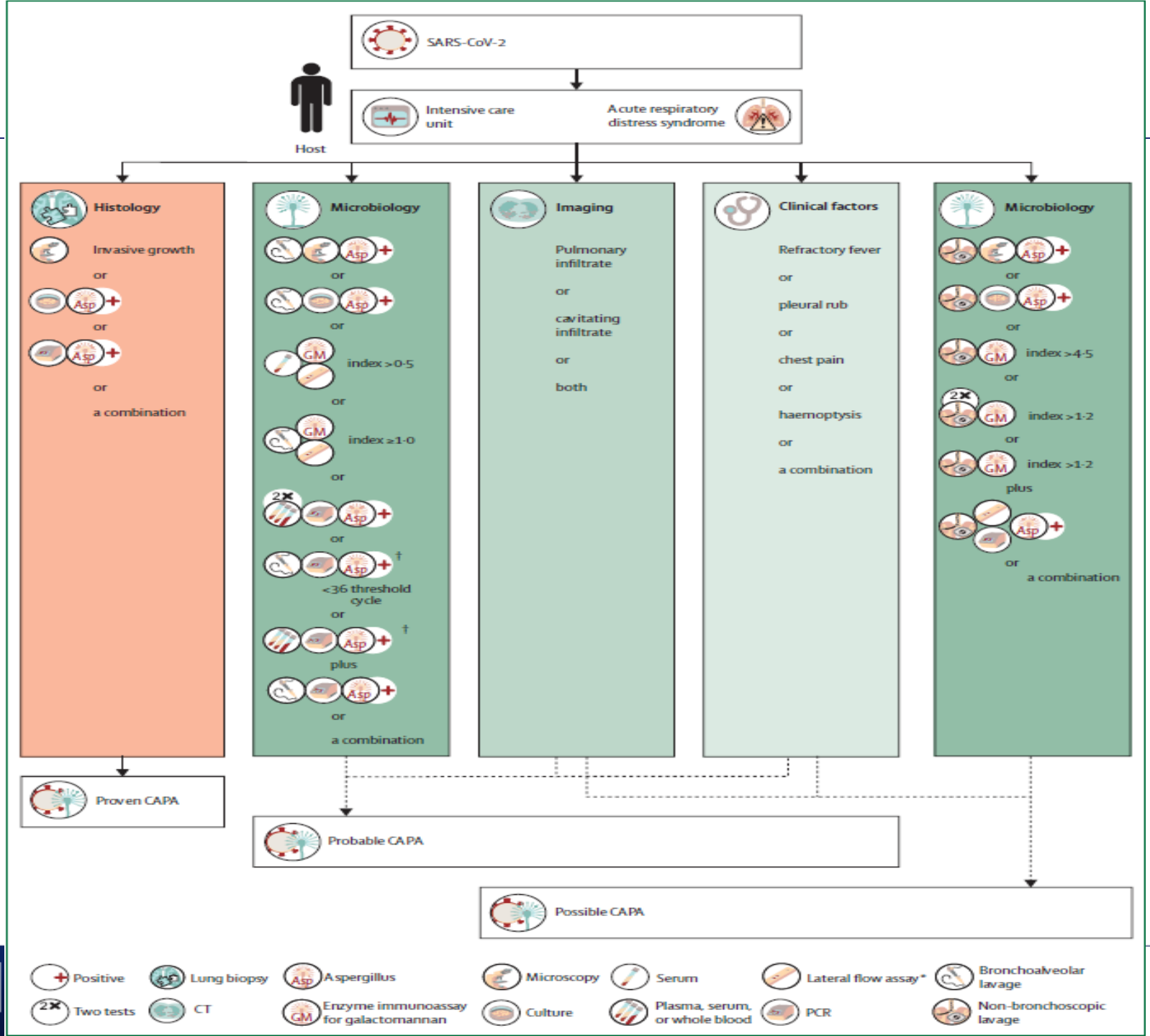
Woon Hean Chong[1] · Biplab K. Saha[2] · Kristoffer P. Neu[3]

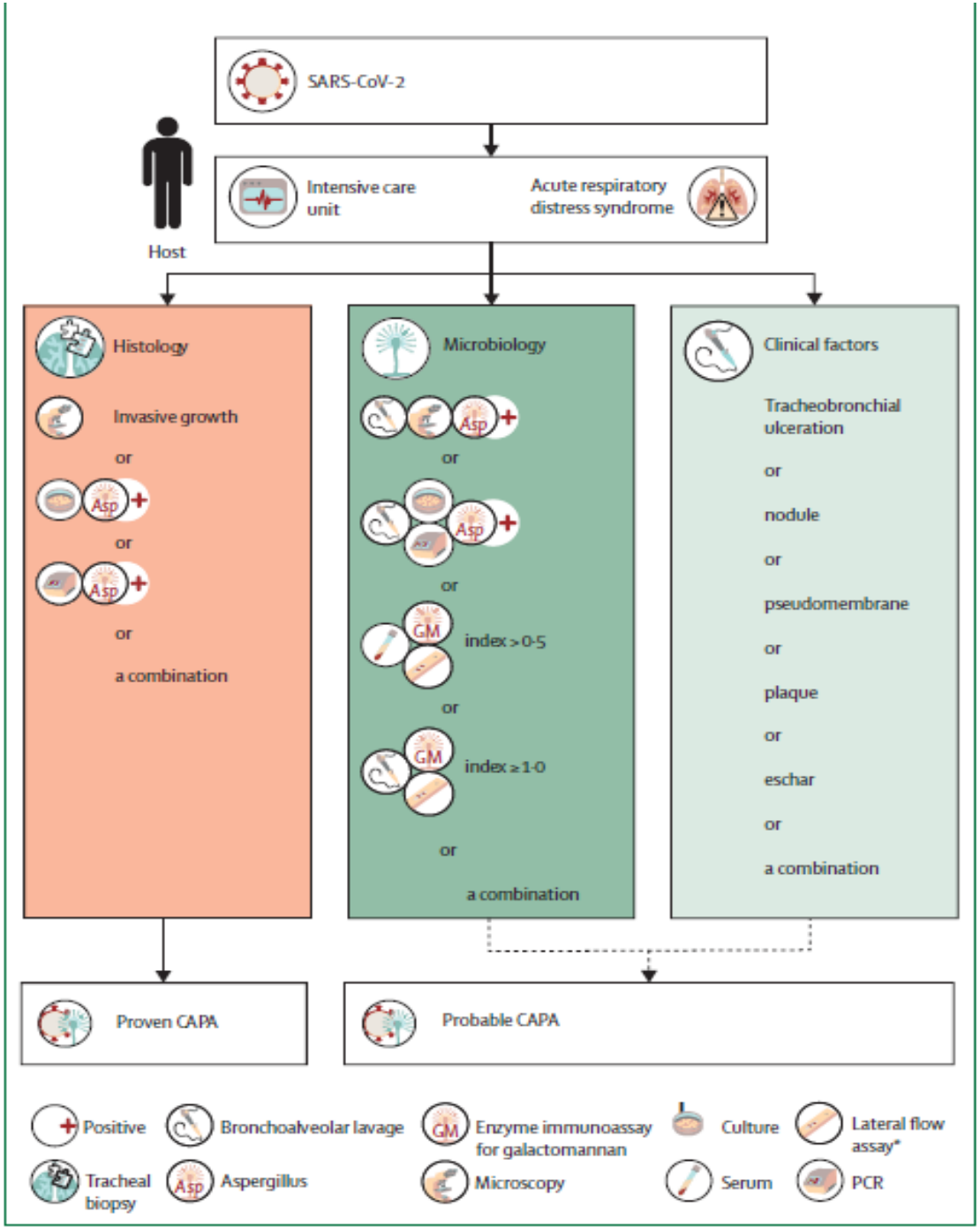
Variables	Studies (*N*)	CAPA	No CAPA	OR/MD	95% CI	*P* value	Heter genei (I^2)
Clinical characteristics							
Age (Y) Mean ± S.D	8	66.58 ± 4.55	59.25 ± 3.42	MD 7.52	2.02–13.03	0.007	74%
Male	7	72.5% (74/102)	70.6% (291/412)	OR 0.82	0.43–1.55	0.54	27%
BMI (kg/m^2) Mean ± S.D	4	27.80 ± 1.71	27.88 ± 0.74	MD − 0.46	[− 1.93, 1.02]	0.54	46%
Comorbidities							
COPD	7	13.7% (14/102)	6.1% (25/412)	OR 2.75	1.00–7.52	0.05	38%
Diabetes	7	26.5% (27/102)	23.3% (94/404)	OR 1.20	0.71–2.01	0.49	0%
Cancer	4	8.2% (5/61)	3.7% (10/271)	OR 2.25	0.68–5.07	0.14	0%
Long-term medications							
Long-term corticosteroid	3	15.0% (9/60)	5.3% (10/190)	OR 3.53	1.16–10.69	0.03	9%
Long-term immunosuppressants	2	10.0% (3/30)	7.1% (8/112)	OR 1.87	0.28–12.29	0.52	25%
COVID-19 therapies							
Initial antibiotic treatment	5	82.5% (52/63)	81.6% (391/479)	OR 0.88	0.39–1.97	0.75	12%
Initial corticosteroid treatment	4	49.2% (30/61)	66.8% (300/449)	OR 0.69	0.19–2.58	0.58	73%
Tocilizumab	4	55.4% (41/74)	38.9% (171/440)	OR 1.85	0.88–3.89	0.10	18%
Hydroxychloroquine	4	70.3% (52/74)	81.6% (359/440)	OR 0.43	0.07–2.68	0.36	84%
ICU A = admission							
Illness onset to ICU admission (D) mean ± S.D	2	11.00 ± 2.50	12.00 ± 3.00	MD − 1.00	[− 1.66, − 0.34]	0.003	0%
SOFA Score mean ± S.D	3	9.37 ± 2.02	7.27 ± 1.32	MD 2.57	1.46–3.68	< 0.001	0%
Outcomes							
Mortality	7	42.6% (43/101)	26.5% (139/524)	OR 3.39	1.97–5.86	< 0.001	0%
ICU LOS (D) mean ± S.D	6	25.72 ± 7.19	18.44 ± 4.06	MD 6.85	[− 2.08, 15.79]	0.13	84%
IMV duration (D) mean ± S.D	3	17.00 ± 2.94	16.00 ± 0.82	MD − 1.66	[− 5.49, 2.16]	0.39	0%
RRT	4	37.1% (26/70)	19.1% (54/282)	OR 2.30	0.95–5.57	0.06	42%
Inotropic support	3	79.0% (49/62)	75.8% (141/186)	OR 1.19	0.56–2.56	0.65	0%

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

Koehler P et al. Lancet Infect Dis Dec 14, 2020

Host factors	Clinical factors	Mycological evidence	Comments
(Continued from previous page)			
Proposed case definition for CAPA (adapted from EORTC and MSGERC[3], AspICU[47], and expert case definitions of IAPA[48])			
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)†
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)


SARS-CoV-2
Host
Intensive care unit
Acute respiratory distress syndrome
Histology
Invasive growth
or
Asp +
or
Asp +
or
a combination
Proven CAPA
Microbiology
Asp +
or
Asp +
or
GM index >0·5
or
GM index ≥1·0
or
2✕ Asp +
or
Asp + †
<36 threshold cycle
or
Asp + †
plus
Asp +
or
a combination
Probable CAPA
Imaging
Pulmonary infiltrate
or
cavitating infiltrate
or
both
Clinical factors
Refractory fever
or
pleural rub
or
chest pain
or
haemoptysis
or
a combination
Microbiology
Asp +
or
Asp +
or
GM index >4·5
or
2✕ GM index >1·2
or
GM index >1·2
plus
Asp +
or
a combination
Possible CAPA
Positive
2✕ Two tests
Lung biopsy
CT
Asp Aspergillus
GM Enzyme immunoassay for galactomannan
Microscopy
Culture
Serum
Plasma, serum, or whole blood
Lateral flow assay*
PCR
Bronchoalveolar lavage
Non-bronchoscopic lavage


SARS-CoV-2
Host
Intensive care unit
Acute respiratory distress syndrome
Histology
Invasive growth
or
Asp
or
Asp
or
a combination
Microbiology
Asp
or
Asp
or
GM
index > 0·5
or
GM
index ≥ 1·0
or
a combination
Clinical factors
Tracheobronchial ulceration
or
nodule
or
pseudomembrane
or
plaque
or
eschar
or
a combination
Proven CAPA
Probable CAPA
Positive
Bronchoalveolar lavage
GM
Enzyme immunoassay for galactomannan
Culture
Lateral flow assay*
Tracheal biopsy
Asp
Aspergillus
Microscopy
Serum
PCR

Letter to the Editor

COVID-19-associated pulmonary aspergillosis (CAPA): how big a problem is it?

Arnaud Fekkar [1,*], Dionysios Neofytos [2], Minh-Hong Nguyen [3], Cornelius J. Clancy [3], Dimitrios P. Kontoyiannis [4,†], Frederic Lamoth [5,†]

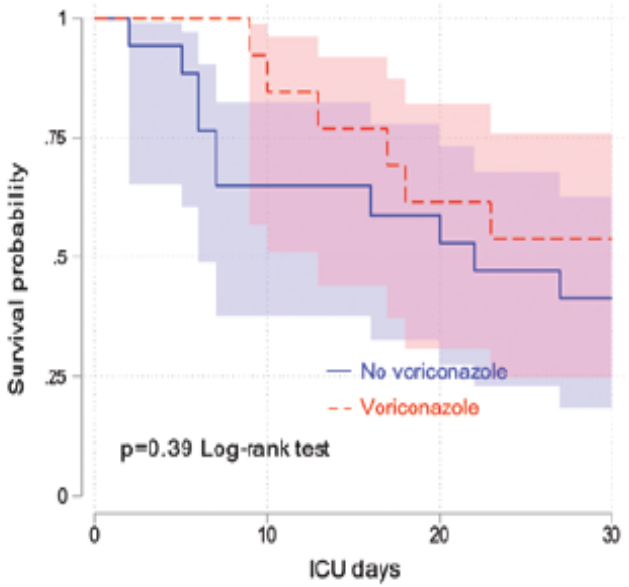
Incidence of CAPA (COVID-19-associated pulmonary aspergillosis) among non-immunocompromised patients in published cohorts according to definition criteria

Consideration of publications in the paper by Koehler et al.	References	Date of online availability	Incidence of COVID-19-associated aspergillosis reported by the authors[a]	Incidence of proven/probable cases according to Koehler et al.	Incidence of possible cases according to Koehler et al.
Publications referenced in the paper by Koehler et al.	Koehler et al. [3]	15th May 2020	26.3% (5/19)	21.1% (4/19)	0% (0/19)
	Alanio et al. [2]	29th May 2020	30.8% (8/26)	19.2% (5/26)	3.8% (1/26)
	Rutsaert et al. [16]	1st June 2020	31.6% (6/19)	26.3% (5/19)	5.3% (1/19)
	Van Arkel et al. [4]	1st July 2020	19.4% (6/31)	9.7% (3/31)	6.5% (2/31)
	Heard et al. [13][b]	3rd July 2020	0% (0/57)	0% (0/57)	1.8% (1/57)
	Gangneux et al. [6]	10th July 2020	20.0% (9/45)	Not calculable	Not calculable
	Nasir et al. [5]	18th July 2020	21.7% (5/23)	0% (0/23)	21.7% (5/23)
	Bartoletti et al. [7]	28th July 2020	28.2% (29/103)	28.2% (29/103)	0% (0/103)
	White et al. [8]	29th August 2020	14.1% (19/135)	2.2% (3/135)	8.1% (11/135)
	Subtotal		**19.0% (87/458)**	**11.9% (49/413)**	**5.1% (21/413)**
Publications not referenced in the paper by Koehler et al.	Wang et al. [14]	5th June 2020	7.7% (8/104)	3.8% (4/104)[c]	3.8% (4/104)
	Lamoth et al. [11]	10th July 2020	3.8% (3/80)	1.3% (1/80)	2.5% (2/80)
	Brown et al. [12]	6th August 2020	0% (0/60)	0% (0/60)	6.7% (4/60)
	Subtotal		**4.5% (11/244)**	**2.0% (5/244)**	**4.1% (10/244)**
Publications not available at the time the paper by Koehler et al. was written	Dupont et al. [19]	10th September 2020	17.9% (19/106)	8.5% (9/106)	7.5% (8/106)
	Chauvet et al. [18]	11th November 2020	9.8% (4/41)	4.9% (2/41)	0% (0/41)
	Roman-Montes et al. [21]	20th November 2020	9.7% (14/144)	3.5% (5/144)	6.3% (9/144)
	Fekkar et al. [20]	2nd December 2020	2.4% (3/125)	1.6% (2/125)[d]	0.8% (1/125)
	Segrelles-Calvo et al. [22]	3rd December 2020	3.3% (7/215)	2.8% (6/215)[c]	0.5% (1/215)
	Subtotal		**7.4% (47/631)**	**3.8% (24/631)**	**3.0% (19/631)**
All publications	**Total**		**10.9% (145/1333)**	**6.1% (78/1288)**	**3.9% (50/1288)**

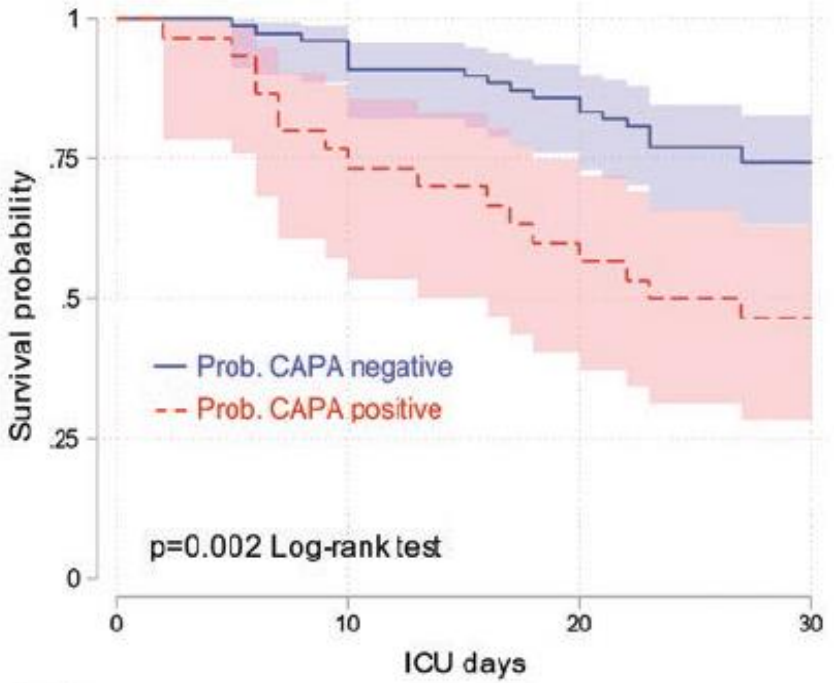
Epidemiology of Invasive Pulmonary Aspergillosis Among Intubated Patients With COVID-19: A Prospective Study

Michele Bartoletti,[1] Renato Pascale,[1] Monica Cricca,[2] Matteo Rinaldi,[1] Angelo Maccaro,[1] Linda Bussini,[1] Giacomo Fornaro,[1] Tommaso Tonetti,[3] Giacinto Pizzilli,[3] Eugenia Francalanci,[1] Lorenzo Giuntoli,[4] Arianna Rubin,[1] Alessandra Moroni,[2] Simone Ambretti,[2] Filippo Trapani,[1] Oana Vatamanu,[1] Vito Marco Ranieri,[3] Andrea Castelli,[5] Massimo Baiocchi,[5] Russell Lewis,[1] Maddalena Giannella,[1] and Pierluigi Viale[1]; for the PREDICO Study Group[a]

A



Number at risk				
No voriconazole	17	11	10	7
Voriconazole	13	12	8	7



Number at risk				
Prob. negative	78	75	67	58
Prob. positive	30	23	18	14

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

What is the optimal approach towards diagnosing or refuting CAPA in patients with COVID-19?

Recommendations	Strength of recommendation	Quality of evidence
A CAPA **diagnostic work-up** is **recommended** in mechanically ventilated COVID-19 patients with unexplained respiratory deterioration or a positive *Aspergillus* culture from the respiratory tract	Strong	Low
Standard **CT imaging** is **not recommended** to refute or diagnose CAPA	Weak	Very low
Screening of critically ill COVID-19 patients for serum GM or BDG is **not recommended**	Strong	Low
Detection of *Aspergillus* in sputum and tracheal aspirate is considered **insufficient evidence** to support CAPA diagnosis, but warrants further diagnostics through bronchoscopy and BAL	Strong	Low
We **recommend** maximum efforts to perform a **bronchoscopy** for inspection of the airways and **bronchoalveolar lavage** (BAL) to diagnose CAPA in patients with proven or high likelihood of COVID-19 in the ICU	Strong	Low
There is **no recommendation against or in favor** of using **lateral flow devices-based assays** for diagnosing CAPA	Weak	Very low

Verveji PE et al.

Intensive Care Med (2021) 47:819–834

Antifungal prophylaxis for prevention of COVID-19-associated pulmonary aspergillosis in critically ill patients: an observational study

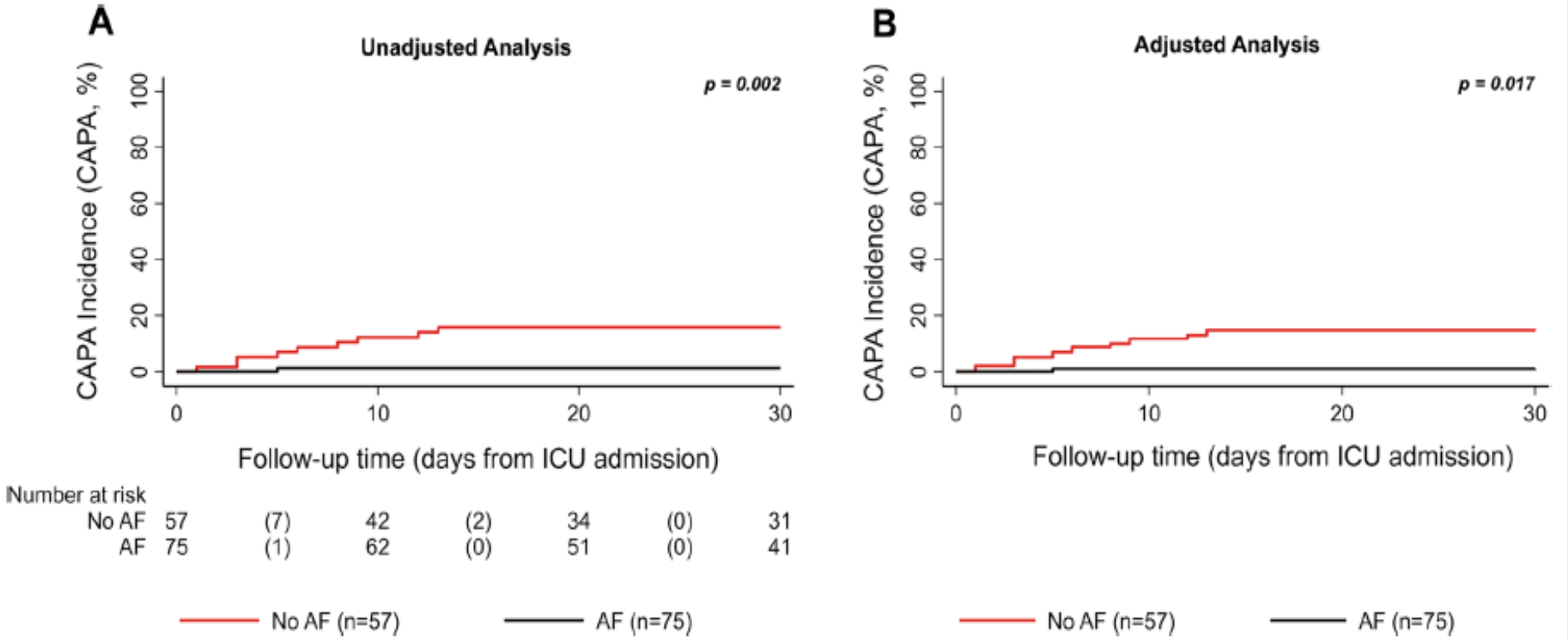


Fig. 2 CAPA incidence according to antifungal prophylaxis. 30-day CAPA incidence in patients without (red curve) and with (black curve) mould active antifungal prophylaxis. A competing risk analysis was performed as death is a competing risk for development of CAPA. Panel **A** denotes the unadjusted analysis (17.5 vs 1.4%, $p = 0.002$). Panel **B** denoted the IPTW weighted (adjusted) analysis (15.8 vs 1.1%, $p = 0.002$). Abbreviation: AF antifungal prophylaxis; CAPA COVID-19-associated pulmonary aspergillosis; ICU intensive care unit

Hatzl S et al. Crit Care 2021;25:335

Antifungal prophylaxis for prevention of COVID-19-associated pulmonary aspergillosis in critically ill patients: an observational study

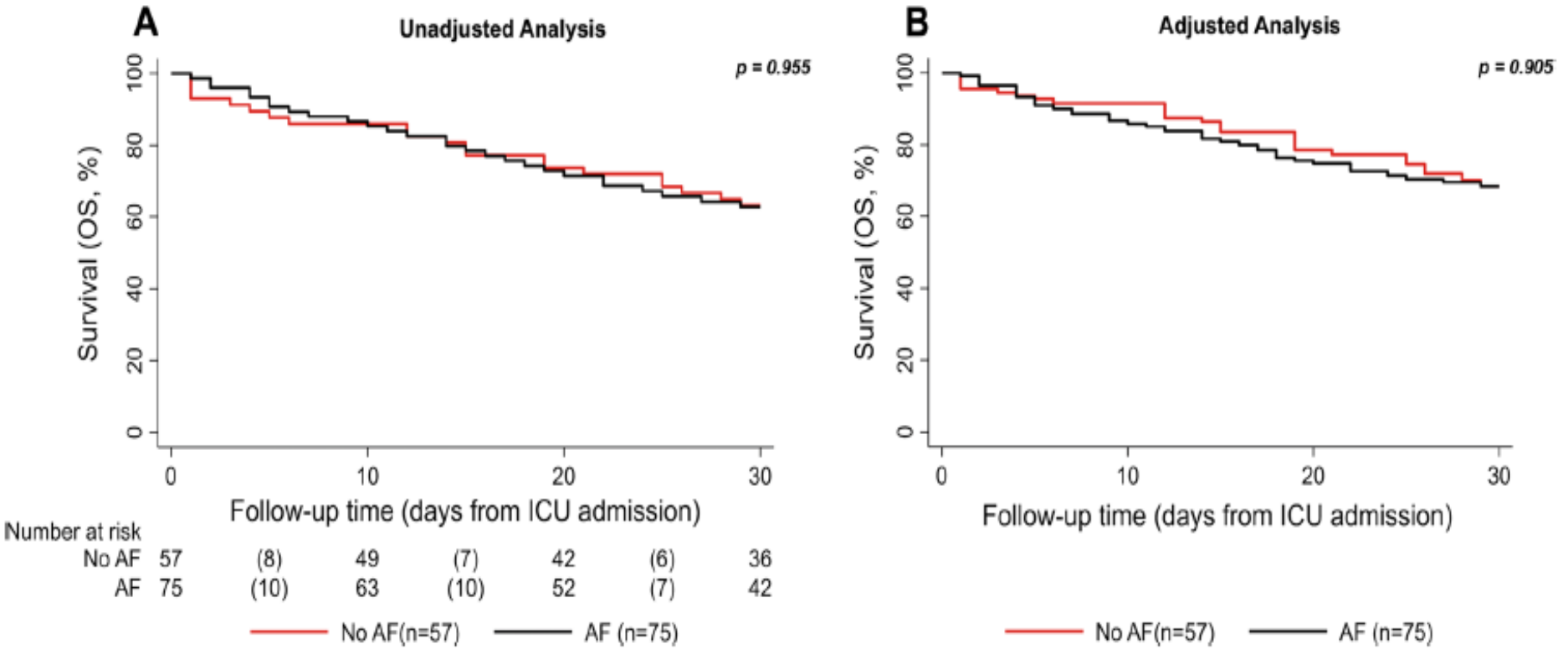


Fig. 3 30-day ICU survival according to antifungal prophylaxis. **A** Unadjusted analysis, **B** IPTW adjusted analysis. *p* values are calculated using the log rank test. Risk table was only computed for the unadjusted analysis. ICU survival was calculated by using Kaplan–Maier estimators. CAPA coronavirus disease 19-associated pulmonary aspergillosis; AF antifungal prophylaxis

Hatzl S et al. Crit Care 2021;25:335

Conclusions

The real incidence of CAPA is presently unknown

There are too many proposed case definitions but there is no agreement about which is the the best to be used

Fungal biomarkers for diagnosis of pulmonary aspergillosis in patients affected by SARS-CoV-2 are less helpful than in other clinical conditions (colonization vs angioinvasive disease)

Autopsy proven aspergillosis is rarely reported and the cumulative prevalence seems to be lower than observed in *ex-vivo* studies