Cavitary Lung Disease After COVID 19

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Radiological Features of COVID 19

early stages

peripheral, bilateral, ground-glass opacities

peak stages

consolidation, septal thickening, crazy-paving pattern, halo sign, nodules and reversed halo sign

Late stages

pleural effusion, lymphadenopathy, tree-in-bud sign, pericardial effusion, and cavitating lung lesions

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BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Pulmonary cavitation: an under-recognized late complication of severe COVID-19 lung disease

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Results

- 12 out of 689 (1.7%) patients with COVID-19 developed pulmonary cavitation,
- 3.3% (n=12/359) of patients who developed COVID-19 pneumonia,
- 11% (n=12/110) of those admitted to the intensive care unit.
- In this cohort six patients have died, and six discharged home

Patient Characteristic

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Age range	50–59	40–49	60–69	40–49	60–69	50–59	40–49	30–39	40–49	50–59	30–39	40–49
BMI	30.9	30.4	31.3	29.2	25.1	29.4	26.3	21.5	30.1	19.8	24	27.7
Comorbidities	DM, HT	HT	DM	DM	COPD	HT	HT		DM, HT	DM	DM	DM
On admission												
Time from symptom onset to intubation (days)	6	12	9	7	5	5	8	15	3	9	10	8
P/F ratio	48.8	41.6	49.7	33.0	46.1	47.0	65.3	41.8	70.5	100.1	109.4	104.5
SOFA score (points)	24	21	24	25	23	23	16	21	25	23	18	17
Neutropenia											Y	
Leucocytes (× 10*9/L)	0.49	1.35	0.3	2.78	0.6	1.1	1.66	1.03	0.46	2.91	1.62	2.63
During the admission												
NM blockade	Y	Y	Y	Y	Y	Y	Y	Y	Y			Y
VTE		DVT and PE				PE	DVT			DVT		
CVA	Y									Y		
CRRT/IHD		Y	Y	Y	Y	Y			Y			Y
ECMO							Y	Y	Y			
Proned	Y	Y	Y	Y	Y	Y		Y	Y	Y		
Tracheostomy	Y		Y	Y	Y	Y	Y	Y	Y			
Days of systemic CS	17	15	19	24	11	14	14	25	18	9	6	5
+ ve fungal cultures or serology		Y	Y	Y		Y			Y			
Treated for fungal infection	Y	Y	Y	Y		Y	Y		Y			Y
Duration of hospital stay (days)	37	25	53	33	53	74	101	133	57	56	47	40
Outcome												
	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Discharged home	Discharged home	Discharged home	Discharged home	Discharged home	Discharged home

Characteristic of pulmonary cavities

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
No. of cavities (n)	1	8	8	3	1	1	2	1	9	3	1	5
Largest cavity (mm)	50	85	60	30	30	30	70	100	54	52	50	40
Bilateral		Y	Y	Y			Y		Y	Y		Y
Location of cavities												
No. lobes with cavities (n)	1	5	5	3	1	4	2	1	4	3	1	3
RUL		Y	Y	Y				Y	Y	Y	Y	
RML		Y	Y		Y	Y			Y			
RLL		Y	Y			Y	Y		Y	Y		Y
LUL		Y	Y	Y		Y	Y		Y			Y
LLL	Y	Y	Y	Y		Y				Y		Y
Clinical events												
Developed pneumothorax				Y				Y	Y			Y
Developed hemoptysis			Y				Y		Y			Y
Treated for Invasive fungal infection	Y	Y	Y	Y		Y	Y		Y			Y
Bacterial organisms in Sputum/BAL	*K. pneumoniae*	*ECC*	*MRSA*		*S. maltophilia, C. koseri*	*MSSA, S. maltophilia*	*S. marcescens, S. maltophilia, ECC*	*K. pneumoniae*	*Acinetobacter, MRSA*	*ESBL K. pneumoniae, MRSA*	*MRSA*	*K. pneumoniae*

Y yes, *RUL* right upper lobe, *RML* right middle lobe, *RLL* right lower lobe, *LUL* left upper lobe, *LLL* left lower lobe, *BAL* bronchoalveolar lavage, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *K. pneumoniae* Klebsiella pneumonia, *ECC* enterobacter cloacae complex, *S. maltophilia Stenotrophomonas maltophilia*, *S. marcescens Serratia marcescens*, *ESBL* extended spectrum beta-lactamase

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Lung cavitation as a consequence of coronavirus-19 pneumonia

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A retrospective analysis of 206 lung CT scans of patients with SARS-CoV-2 infection. between 01.11.2020 and 31.03.2021
Out of 178 enrolled patients, 6 developed pulmonary cavities (3.37% of all cases).

Male/Female: 4/2
Mean age: 53.66 (35-70)
Cavities Side affected Both/Left/Right 5/1/0
Hospitalization in ICU Yes/No 2/4
All these six patients survived the infection and did not develop pulmonary embolism

Cavitation may be due to:

- Secondary infection,
- Tuberculosis,
- Fungal disease, or
- Pulmonary infarction caused directly by embolic or thrombotic vascular disease related to COVID-19.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D., Axel Haverich, M.D., Tobias Welte, M.D., Florian Laenger, M.D., Arno Vanstapel, Ph.D., Christopher Werlein, M.D., Helge Stark, Ph.D., Alexandar Tzankov, M.D., William W. Li, M.D., Vincent W. Li, M.D., Steven J. Mentzer, M.D., and Danny Jonigk, M.D.

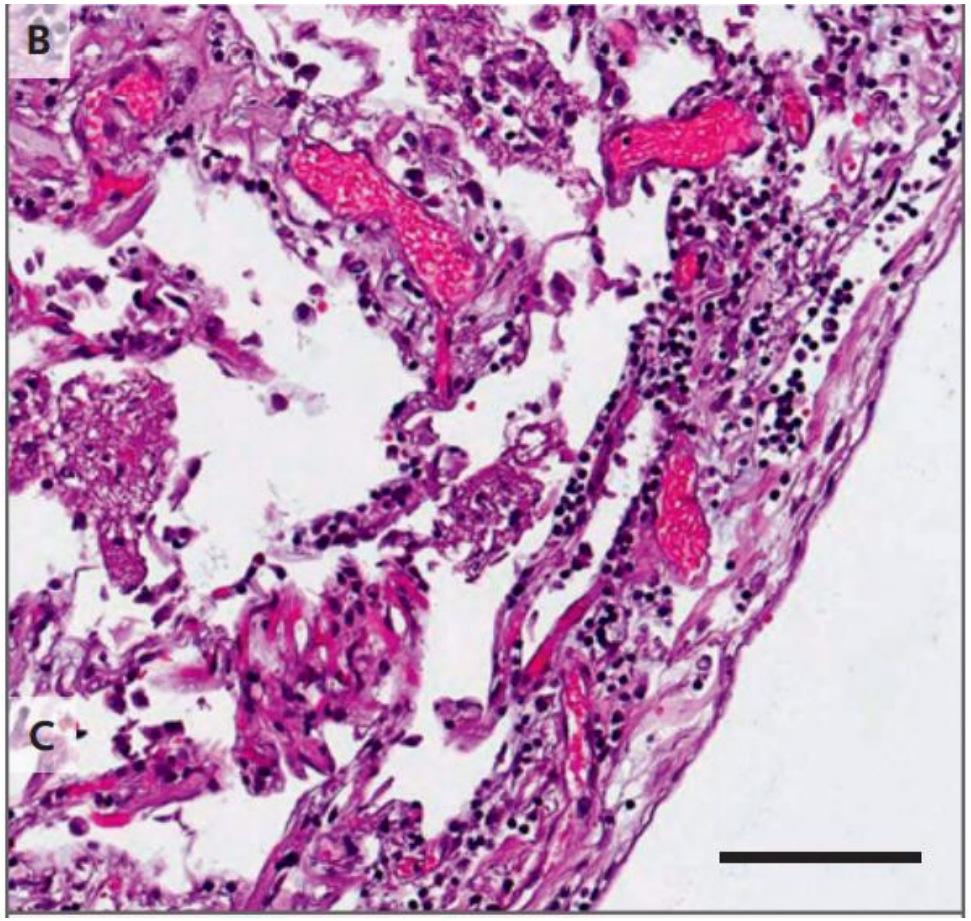
METHODS

- We examined 7 lungs obtained during autopsy from patients who died from Covid-19 and compared them with 7 lungs obtained during autopsy from patients who died from ARDS secondary to influenza A(H1N1) infection and 10 age-matched, uninfected control lungs.
- The lungs were studied with the use of seven-color immunohistochemical analysis, micro–computed tomographic imaging, scanning electron microscopy, corrosion casting, and direct multiplexed measurement of gene expression.

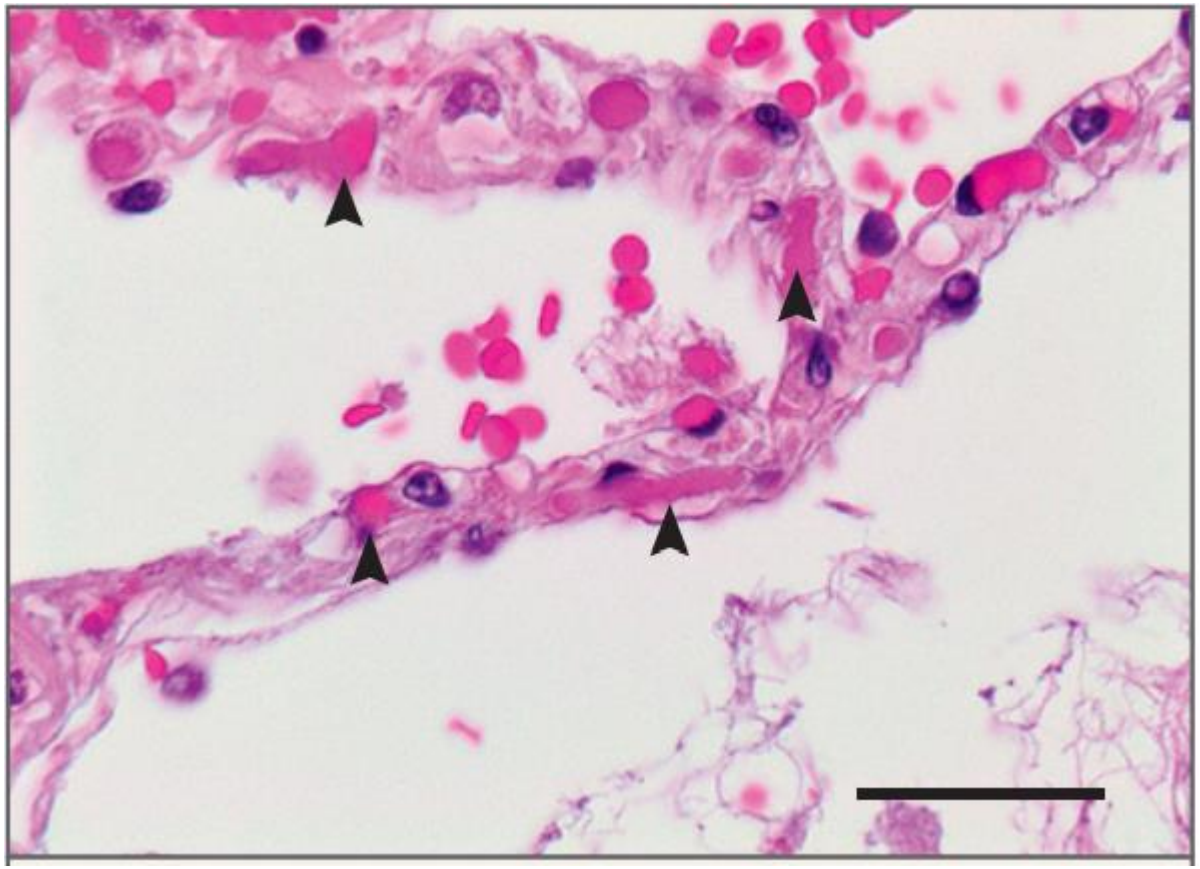
Results

- Diffuse alveolar damage with perivascular T-cell infiltration.
- Severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes.
- Widespread thrombosis with microangiopathy.
- Alveolar capillary microthrombi were 9 times as prevalent in patients with Covid-19 as in patients with influenza ($P<0.001$).
- New vessel growth — predominantly through a mechanism of intussusceptive angiogenesis — was 2.7 times as high as that in the lungs from patients with influenza ($P<0.001$).

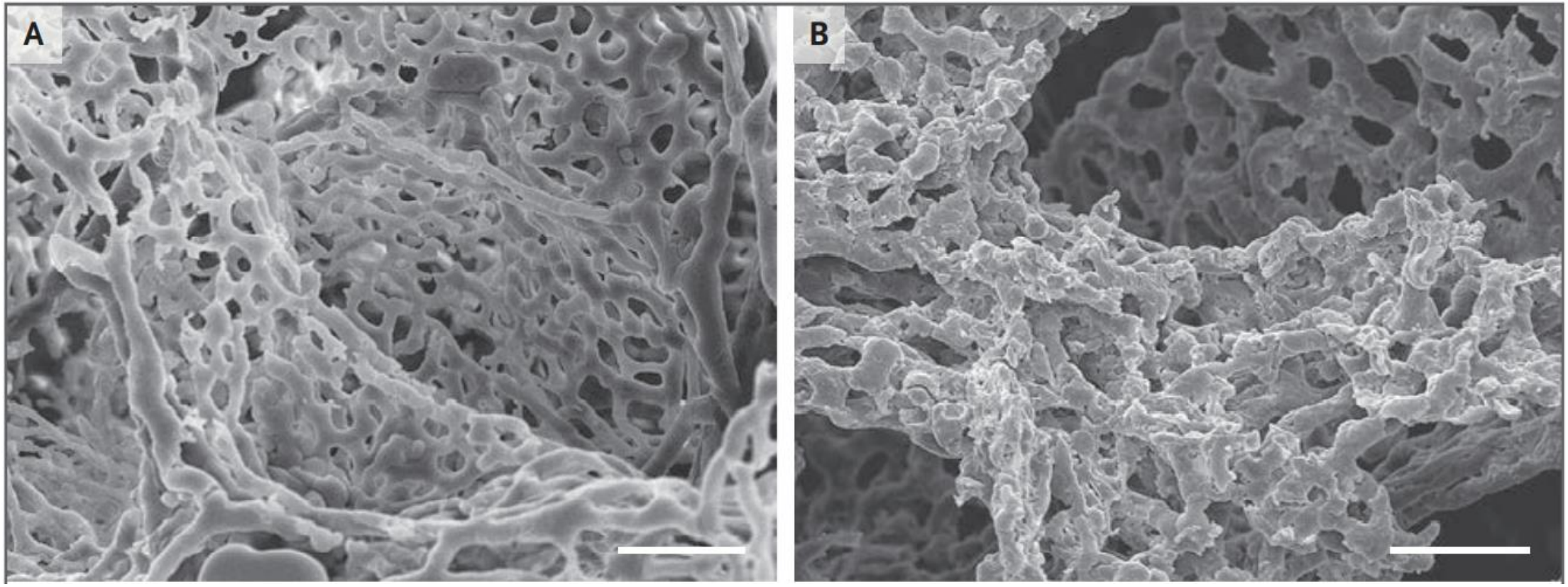
Lymphocytic Inflammation in a Lung from a Patient Who Died from Covid-19

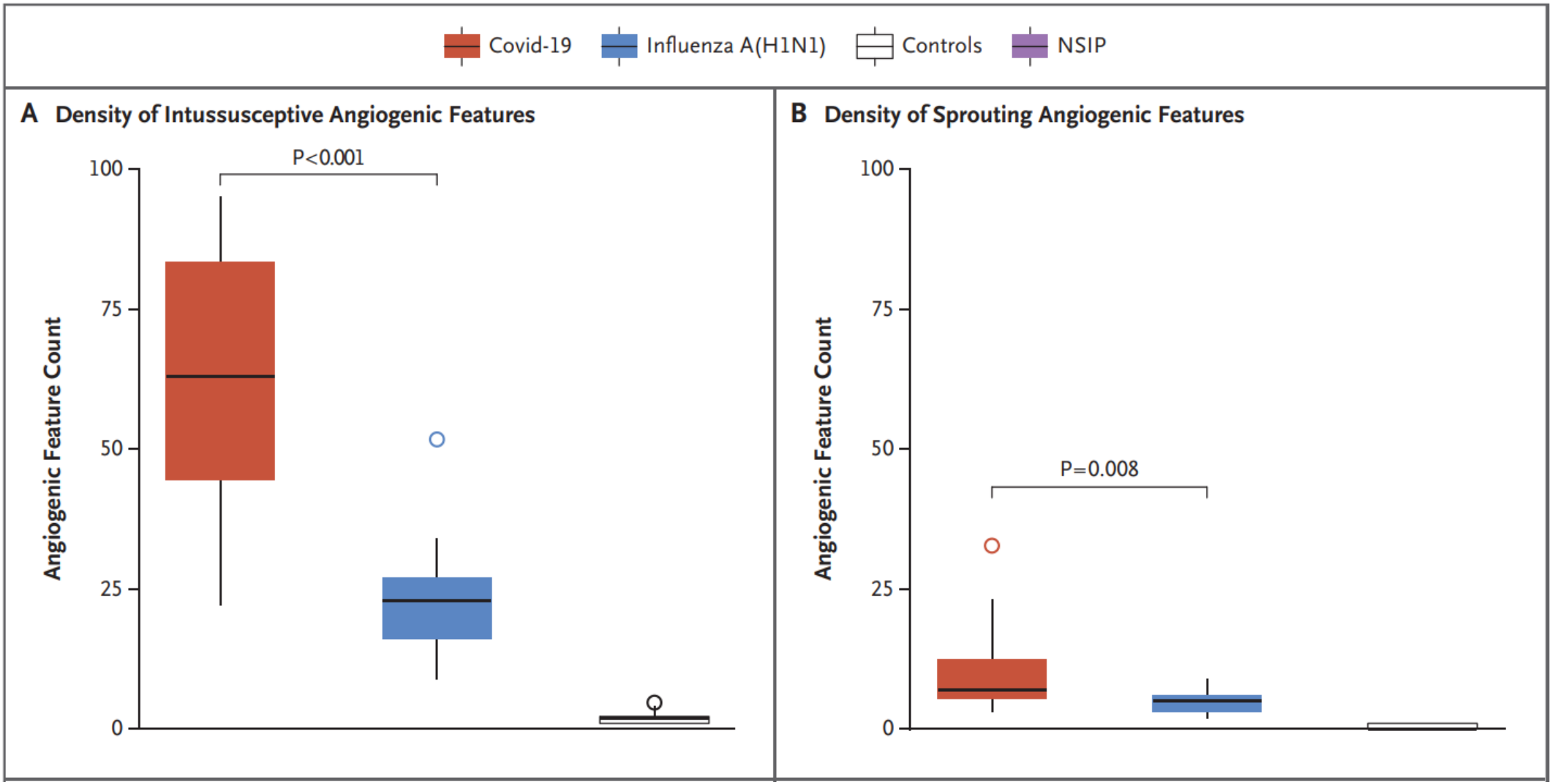


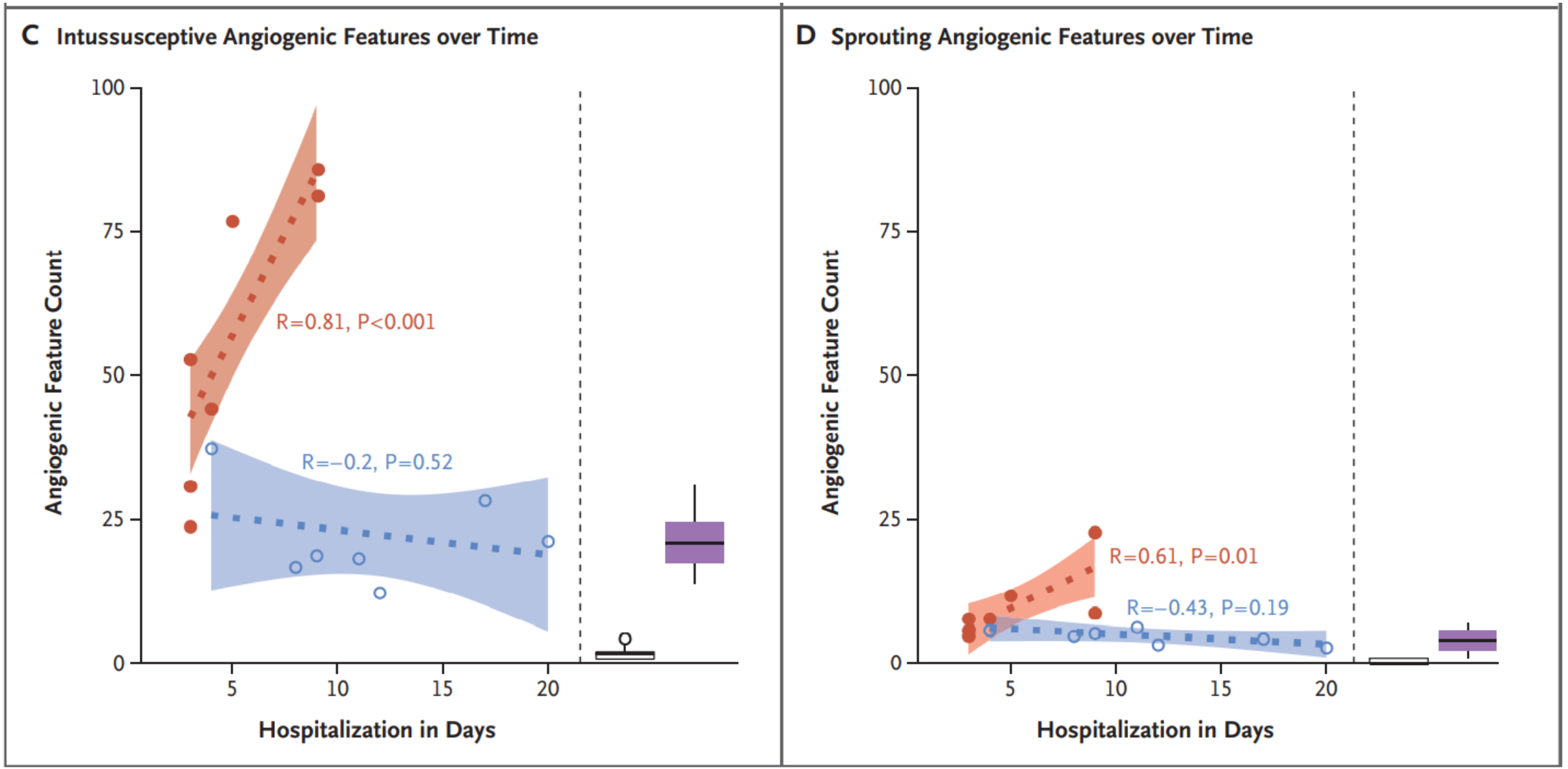
Microthrombi in the Interalveolar Septa of a Lung from a Patient Who Died from Covid-19.



Panels A and B show scanning electron micrographs of microvascular corrosion casts from the thin-walled alveolar plexus of a healthy lung (Panel A) and the substantial architectural distortion seen in lungs injured by Covid-19 (Panel B).




Covid-19
Influenza A(H1N1)
Controls
NSIP
A Density of Intussusceptive Angiogenic Features
P<0.001
Angiogenic Feature Count
100
75
50
25
0
B Density of Sprouting Angiogenic Features
P=0.008
Angiogenic Feature Count
100
75
50
25
0


C Intussusceptive Angiogenic Features over Time
Angiogenic Feature Count
100
75
50
25
0
R=0.81, P<0.001
R=−0.2, P=0.52
5
10
15
20
Hospitalization in Days
D Sprouting Angiogenic Features over Time
Angiogenic Feature Count
100
75
50
25
0
R=0.61, P=0.01
R=−0.43, P=0.19
5
10
15
20
Hospitalization in Days

Review

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

Philipp Koehler, Matteo Bassetti, Arunaloke Chakrabarti, Sharon C A Chen, Arnaldo Lopes Colombo, Martin Hoenigl, Nikolay Klimko, Cornelia Lass-Flörl, Rita O Oladele, Donald C Vinh, Li-Ping Zhu, Boris Böll, Roger Brüggemann, Jean-Pierre Gangneux, John R Perfect, Thomas F Patterson, Thorsten Persigehl, Jacques F Meis, Luis Ostrosky-Zeichner, P Lewis White, Paul E Verweij, Oliver A Cornely, on behalf of the European Confederation of Medical Mycology, the International Society for Human and Animal Mycology, the Asia Fungal Working Group, the INFOCUS LATAM/ISHAM Working Group, the ISHAM Pan Africa Mycology Working Group, the European Society for Clinical Microbiology and Infectious Diseases Fungal Infection Study Group, the ESCMID Study Group for Infections in Critically Ill Patients, the Interregional Association of Clinical Microbiology and Antimicrobial Chemotherapy, the Medical Mycology Society of Nigeria, the Medical Mycology Society of China Medicine Education Association, Infectious Diseases Working Party of the German Society for Haematology and Medical Oncology, and Association of Medical Microbiology and Infectious Disease Canada

Lancet Infect Dis 2021; 21: e149–62

CAPA

- Viral pneumonia increases patients' susceptibility to bacterial and fungal superinfections, including invasive pulmonary aspergillosis (IPA).
- Influenza-associated pulmonary aspergillosis (IAPA) has complicated the clinical course of many critically ill patients with ARDS.
- In a prospective cohort of 108 critically ill patients with ARDS, a higher 30-day mortality was observed in patients with CAPA than in patients without aspergillosis (44% vs 19%).

Incidence

- Autopsy evidence of CAPA has provided low rates of confirmation, with a recent review confirming IFD in only 2% of deceased COVID-19 patients.
- However, this could be indicative of limited tissue and angio-invasion in the CAPA patient, although a recent autopsy study did provide high rates (20%) of proven CAPA.

CAPA: Under-Recognized

- Patients with CAPA might not have host factors and typical radiological features.
- Decreased use of diagnostic bronchoscopy,
- Low sensitivity of detection of circulating galactomannan in serum.
- Further, detection of aspergillus in specimens of the upper respiratory tract, such as sputum or tracheal aspirate, often does not distinguish between aspergillus colonisation and invasive disease.

diagnostic investigations:

- ***CAPA Imaging***
- ***Galactomannan***
- ***(1–3)-β-D-glucan***
- ***lateral flow assays (LFAs)***
- ***Aspergillus PCR***
- ***Non-bronchoscopic lavage***
- ***Fibreoptic Bronchoscopy***

Table 2. Performance of various mycological tests for the diagnosis of COVID-19-associated pulmonary aspergillosis in 68 cases combined from six studies[a] with cases reclassified according to a single case definition[b]

Assay type	Sample type	No of centres performing specific test ($n=6$)	Test positivity rate (%, $n=68$)
Respiratory culture	BAL/NBL/TA	6	65%
Respiratory GM-EIA	BAL/NBL	6	79%
Respiratory *Aspergillus* PCR	BAL/NBL/TA	4	73%
Blood GM-EIA	Serum	6	9%
Blood *Aspergillus* PCR	Serum/plasma	2	21%
Blood BDG	Serum	2	64%

BAL, bronchoalveolar lavage fluid; BDG, (1–3)-β-D-glucan; GM-EIA, galactomannan enzyme-immuno-assay; NBL, nondirected bronchial lavage fluid; TA, tracheal aspirate.

[a]Six studies: [10,18–22].

[b]Single case definition: [10].

Multiple tests

- It confirms no single test generates sensitivity close to 100%, highlighting the potential need for combined testing. Positivity rates are greater when testing respiratory samples, with galactomannan enzyme immunoassay (GMEIA) and Aspergillus PCR providing the greatest sensitivity.
- performing multiple tests (Microscopy/ Culture/GM-EIA/Aspergillus PCR) is recommended.
- Positivity in blood samples is generally lower, reflecting limited invasion by Aspergillus in COVID-19 patients.

Definition of CAPA for clinical studies

- Proven CAPA
- Probable CAPA
- Possible CAPA

Proposed case definition for CAPA (adapted from EORTC and MSGERC , AspICU, and expert case definitions of IAPA

	Host factors	Mycological evidence
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

Proposed case definition for CAPA (adapted from EORTC and MSGERC , AspICU, and expert case definitions of IAPA

	Host factors	Clinical factors	Mycological evidence
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; ▪ bronchoalveolar lavage galactomannan index ≥1·0 or bronchoalveolar lavage LFA index ≥1·0

Proposed case definition for CAPA (adapted from EORTC and MSGERC , AspICU, and expert case definitions of IAPA

	Host factors	Clinical factors	Mycological evidence
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)

Proposed case definition for CAPA (adapted from EORTC and MSGERC , AspICU, and expert case definitions of IAPA

	Host factors	Clinical factors	Mycological evidence
Other pulmonary forms (possible)	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; ▪ non-bronchoscopic lavage galactomannan index >1·2 plus another non-bronchoscopic lavage mycology test positive (non-bronchoscopic lavage PCR or LFA)

Trigger diagnostic investigations for CAPA

- Refractory fever for more than 3 days
- New fever after a period of defervescence of longer than 48 h during appropriate antibiotic therapy.
- Worsening respiratory status (eg, tachypnoea or increasing oxygen requirements);
- Haemoptysis; and pleural friction rub or chest pain can trigger diagnostic investigations for CAPA

in patients with refractory respiratory failure for more than 5–14 days despite receiving all support recommended for patients with COVID-19 who are critically ill

- The median time to CAPA presentation is 10 days (range 0–51 days) post-ICU admission, highlighting the need for prolonged and frequent mycological testing to ensure an earlier diagnosis.
- We recommend either voriconazole or isavuconazole as first-line treatment for possible, probable, and proven CAPA.

Screening

- Serum galactomannan or LFA or LFD, should be considered ***three times per week***, until discharge from ICU or defervescence for longer than 7 days with improved lung function.
- Ideally, this type of screening can be accompanied by regular screening (ie, ***once per week***) of respiratory samples (eg, non-bronchoscopic lavage, tracheal aspirate, or sputum) with culture, PCR, galactomannan or LFA or LFD, with positive tests triggering a CAPA investigation

Check for updates

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ORIGINAL ARTICLE

mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases WILEY

COVID-19-associated subacute invasive pulmonary aspergillosis

Satish Swain[1] | Animesh Ray[1] | Radhika Sarda[1] | Surabhi Vyas[2] | Gagandeep Singh[3] | Pankaj Jorwal[1] | Parul Kodan[1] | Puneet Khanna[4] | Immaculata Xess[3] | Sanjeev Sinha[1] | Naveet Wig[1] | Anjan Trikha[4]

10 patients of (SAIA),
Severe COVID-19 illness with a mean duration of 29.2 ± 12 days from COVID-19 positivity along with cavitary lung disease.
7/10 (70%) patients were known diabetic.
Positive IgG (against Aspergillus)
Serum galactomannan was positive in 5/9 patients (55.5%),
Fungal culture was positive in 2/7 patients (28.5%) and
PCR for Aspergillus was positive in 3 patients.
SAIA should be considered in the differential diagnosis of cavitating lung lesions in patients with recent history of COVID-19 in the background of steroid use with or without pre-existing diabetes.

scientific reports

OPEN

Evidence for a thromboembolic pathogenesis of lung cavitations in severely ill COVID-19 patients

Jan Matthias Kruse[1]✉, Daniel Zickler[1], Willie M. Lüdemann[2], Sophie K. Piper[4], Inka Gotthardt[1], Jana Ihlow[3], Selina Greuel[3], David Horst[3], Andreas Kahl[1], Kai-Uwe Eckardt[1] & Sefer Elezkurtaj[3]✉

- Retrospective study in 39 critically ill adult patients hospitalized with severe acute respiratory syndrome coronavirus 2
- In a tertiary care referral centre during March and May 2020, Berlin/Germany
- Lung cavitation in an unusually large proportion of 22/39 (56%) COVID-19 patients treated on ICU,
- Including 3/5 patients without mechanical ventilation.
- Older and had a higher BMI.
- 19/22 were on mechanical ventilation
- PTE in five patients (12%), 4 with and 1 without lung cavitation.

VILI as a cause

- Ventilator settings did not differ significantly between the groups with and without lung cavities.
- VILI would expect mainly peripheral lesions in the upper lobes, if mechanical overdistension played the main role.
- High percentage of lesions occurred in pre-existing opacities.
- Three of five patients, who did not need mechanical ventilation, also developed cavitation.

Autopsy findings

- pulmonary embolism was more frequent in patients with cavities (4 vs. 1).
- Upon opening the cavities appeared as areas of liquefied necrosis.
- Associations of cavitary lesions with thrombotic occlusion of the supplying pulmonary artery branches.
- Microscopy of adjacent lung tissue revealed numerous thrombotic vascular occlusions and extended, partially haemorrhagic and partially anaemic infarct zones in spatial association with vascular occlusions.
- In summary, macro- and microscopic findings in combination suggested extensive vascular occlusions of different duration with multiple pulmonary infarctions of different size, some of which had transformed into liquefying necrosis, corresponding to large cavities.

Conclusion

- Cavitation is one of the least frequent complications in COVID-19.
- The cavitation mechanism in COVID-19 is unknown and may result from intense inflammatory response leading to diffuse alveolar damage, intraalveolar hemorrhage, and necrosis of parenchyma.
- Appropriate differential diagnosis workup should be done before tying cavity development to COVID-19.
- To date, there is no consensus on how post-COVID-19 cavities should be managed.

References

1- Zaid Zoumot, et al, Pulmonary cavitation: an under-recognized late complication of severe COVID-19 lung disease, BMC Pulm Med (2021) 21:24

2- E. KURYS-DENIS, et al, Lung cavitation as a consequence of coronavirus-19 pneumonia, European Review for Medical and Pharmacological Sciences 2021; 25: 5936-5941

3- Maximilian Ackermann, M.D. et al, Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19, N Engl J Med 2020;383:120-8. DOI: 10.1056/NEJMoa2015432

4- Koehler P, Bassetti M, Chakrabarti A, et al. Defining and managing COVID19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis 2021; 21: e149–e162

5- P. Lewis White, Diagnosis of invasive fungal disease in coronavirus disease 2019: approaches and pitfalls, Curr Opin Infect Dis 2021, 34:573–580

6- Satish Swain, et al, COVID-19-associated subacute invasive pulmonary aspergillosis, Mycoses. 2021;00:1–8.

7- Jan Matthias Kruse,et al, Evidence for a thromboembolic pathogenesis of lung cavitations in severely ill COVID-19 patients, Scientifc Reports | (2021) 11:16039

Thanks For Your Attention