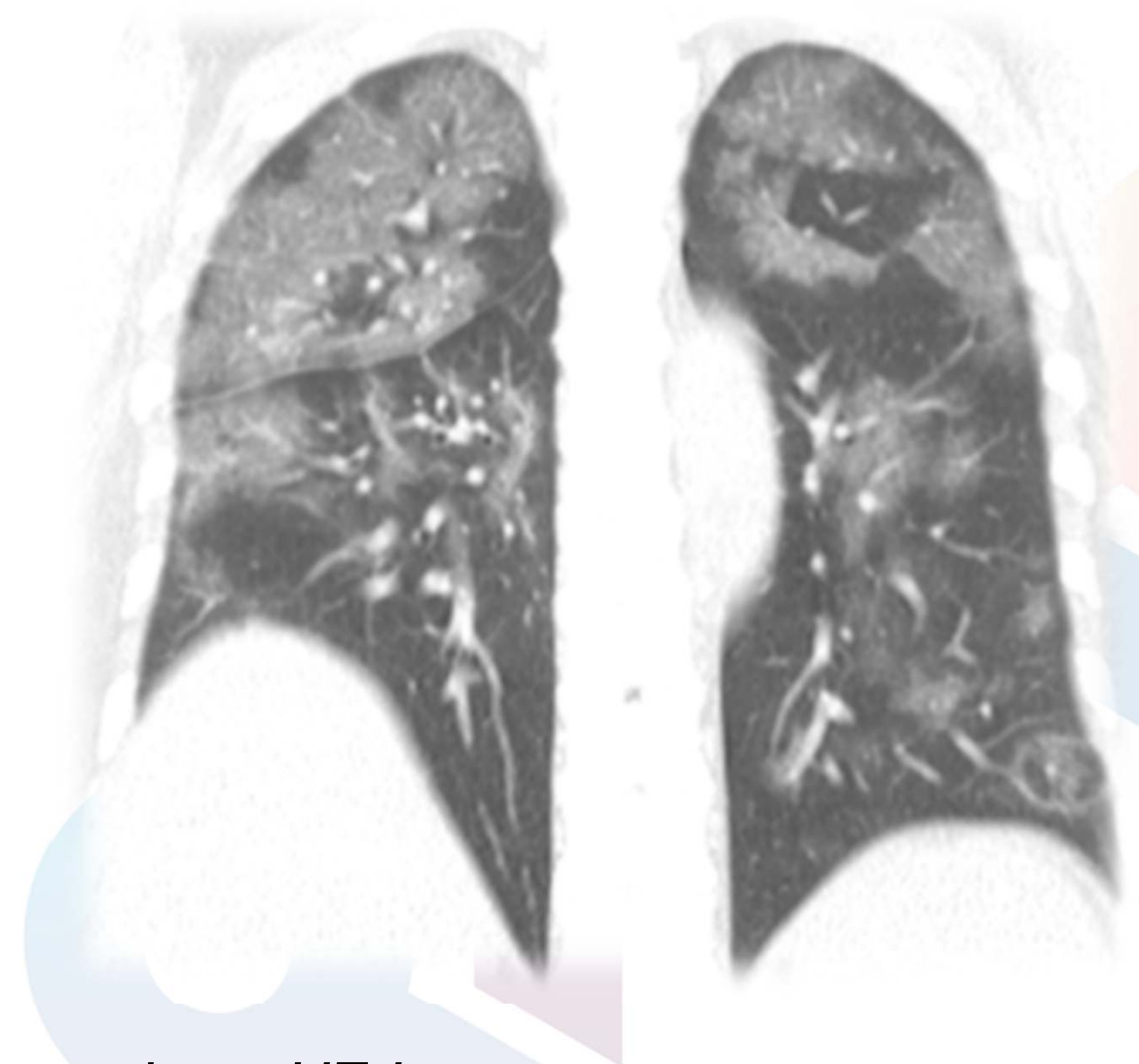


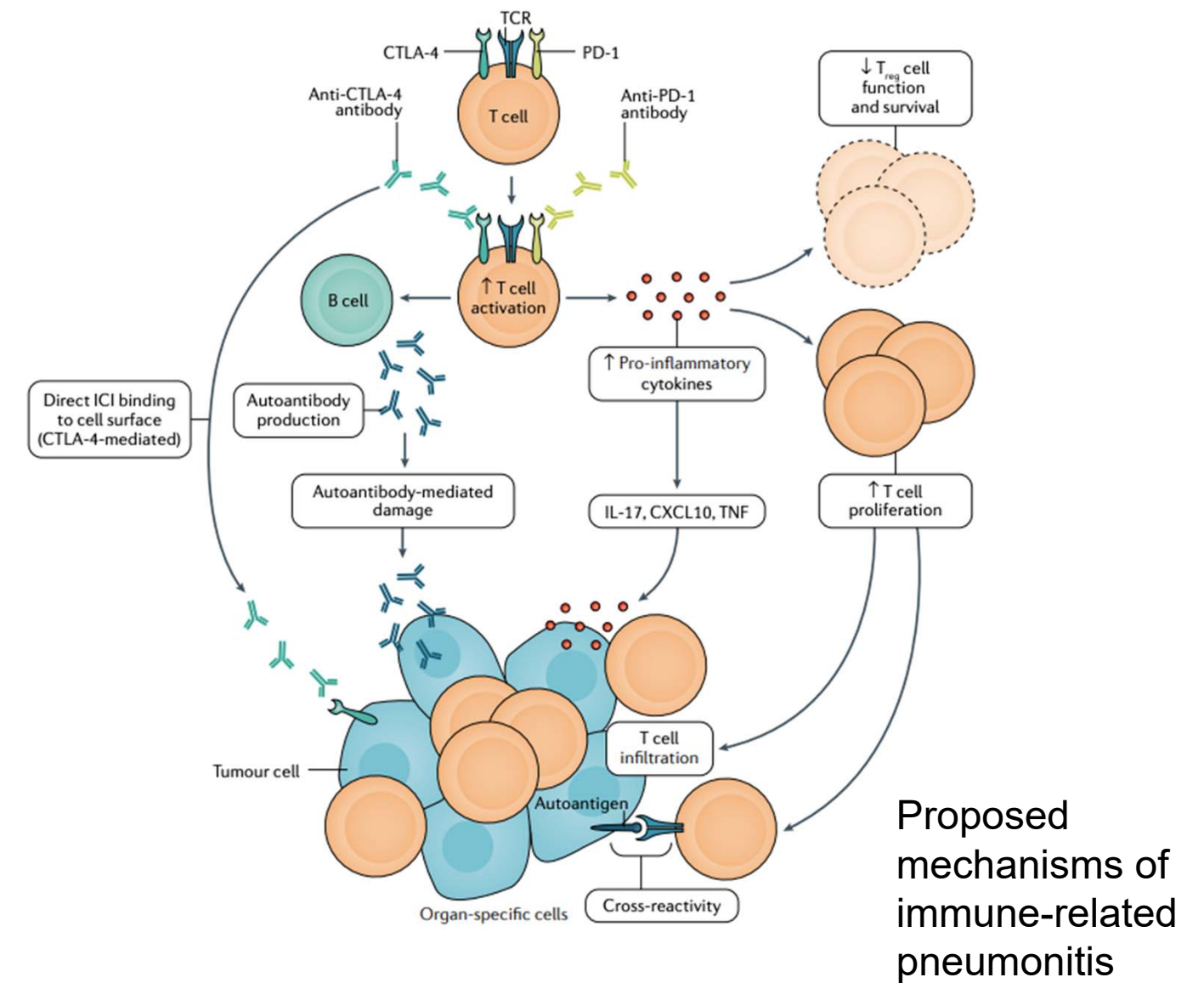
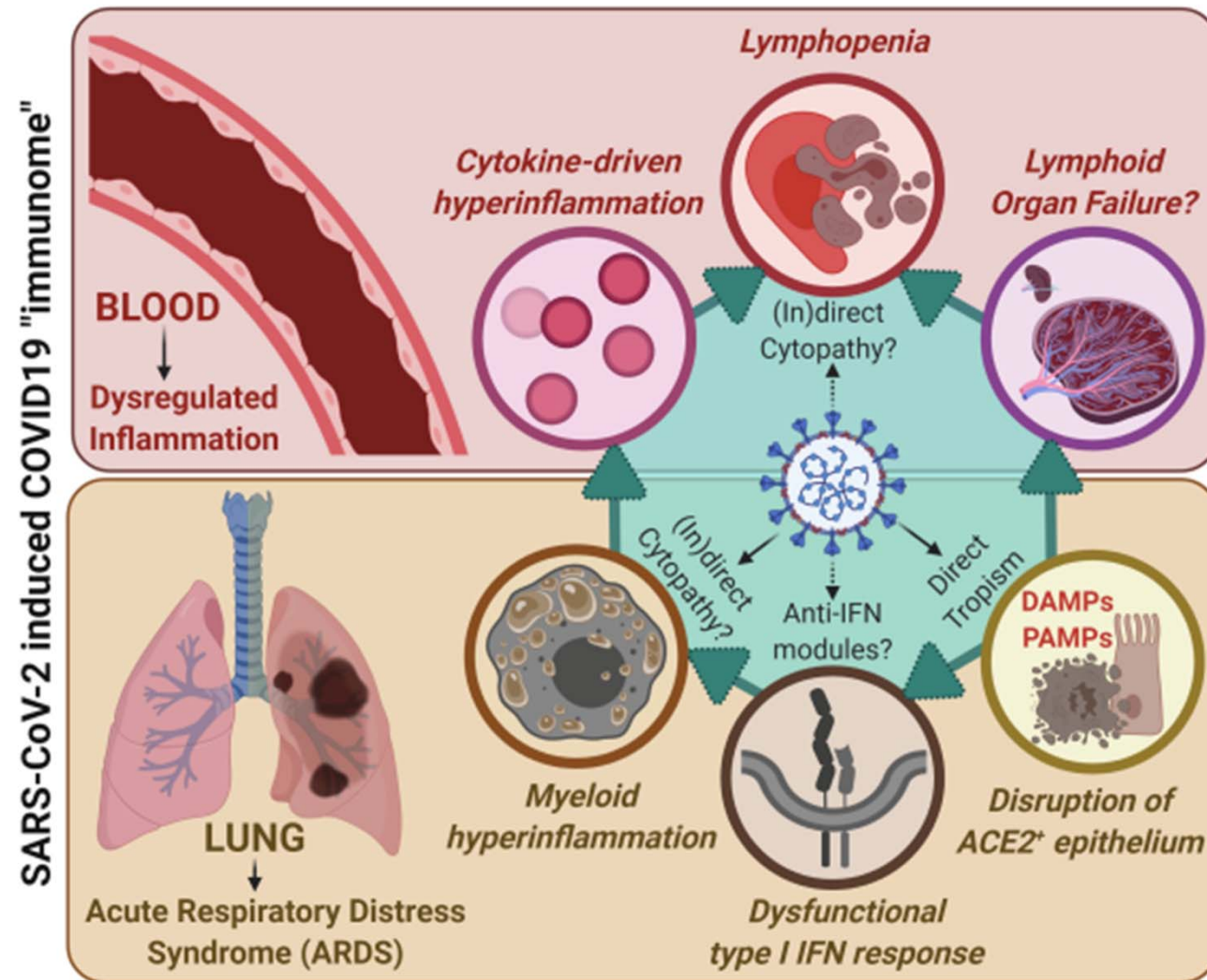
Managing pneumonitis in ICI-treated patients in times of COVID-19

Els Wauters MD, PHD

*Deputy Head of clinic, Respiratory Oncology Unit, Dept. of Pulmonology, UZ Leuven
Senior Academic Staff, Dept. of Chronic Diseases and Metabolism, KU Leuven
Leuven – Belgium*



'Excessive' immune response in common



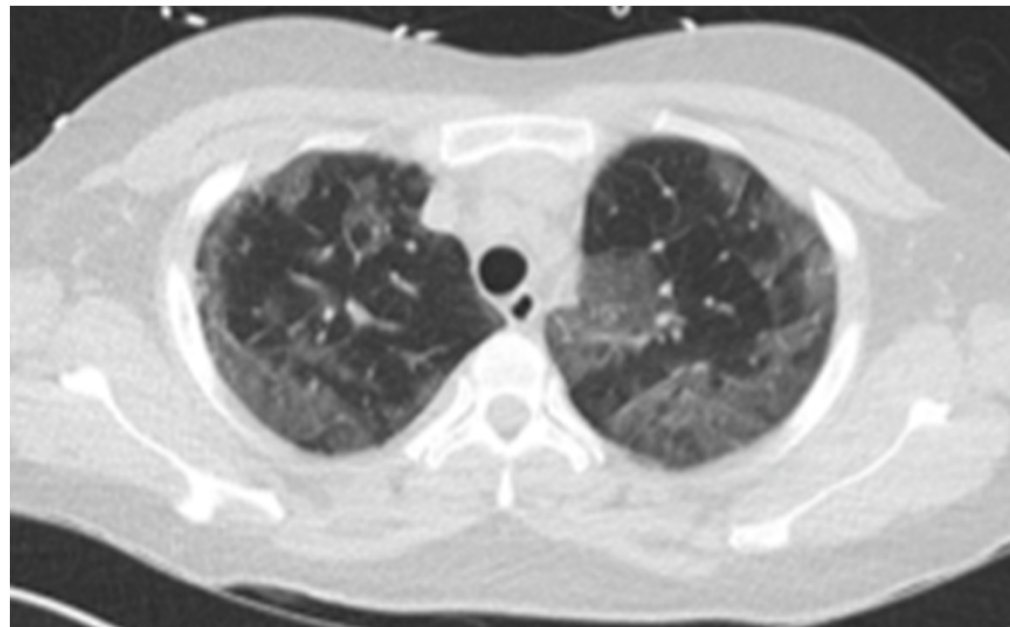
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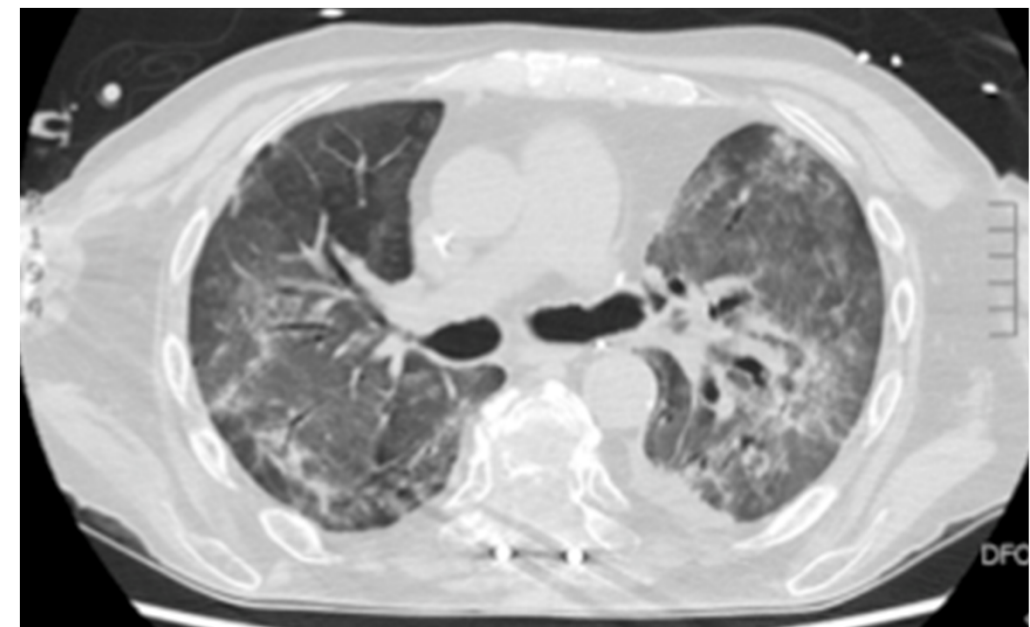
Hyperinflammatory state in the lung in common

Severe COVID-19 pneumonia



Presented with fever, anosmia, shortness of breath and cough

Grade 5 ICI-induced pneumonitis



Presented with shortness of breath and cough

Overlap in clinical and radiological presentation is inevitable: challenging DD



Case study



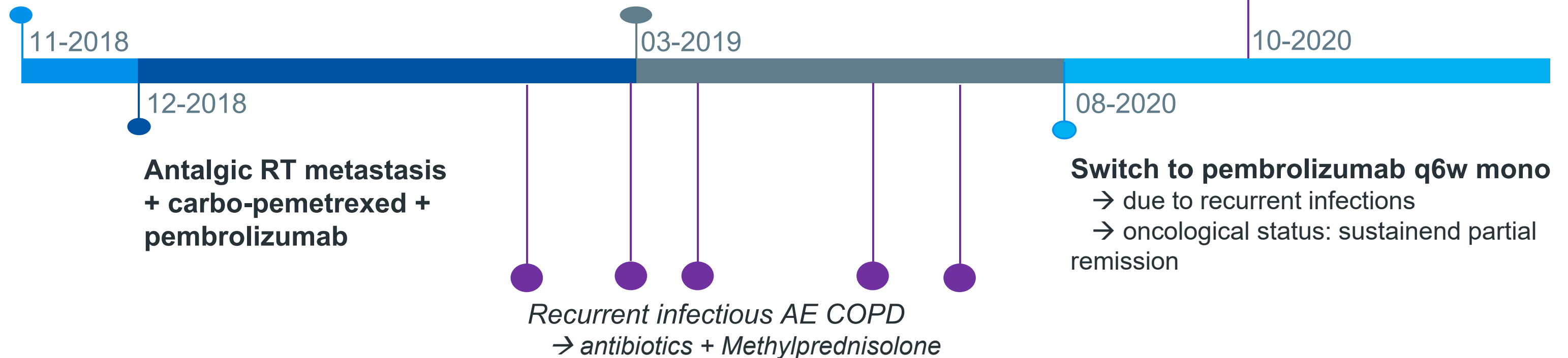
Patient history

Progressive abdominal pain in 58 year old female

- active smoker (30PY)
- COPD GOLD D, treated with ICS/LABA/LAMA

Diagnosis NSCLC cT4N2M1c(muscle)

- KRAS p.G12C-Mt
- PD-L1 IHC 100%



Patient history



History (since 4 days)

Fever (38.7°C)
Lethargy
Progressive dyspnea
Productive cough



Clinical examination

HD stable, 38.2°C, sat.88%
Generally ill appearance
Bilateral ronchi and crackles



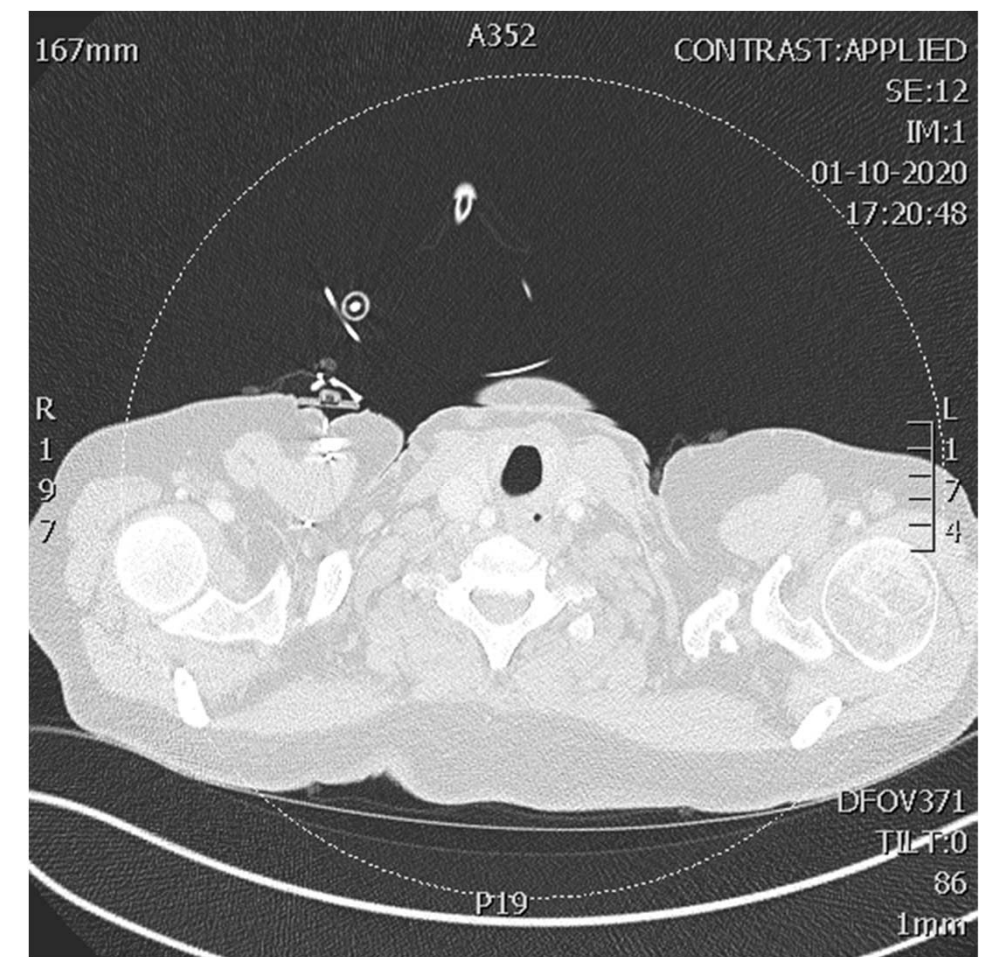
Laboratory results

Lymphopenia $800 \times 10^6/l$
CRP 52mg/l
D-Dimers 952 μ g/l
SARS-CoV-2 PCR negative
(nasopharyngeal swab)



Arterial blood gas

pO₂ 51mmHg with 21% O₂



Patient history



Differential diagnosis

Pneumonitis related to immune checkpoint inhibition

COVID-19 pneumonia

Bacterial pneumonia

Acute exacerbation of COPD

Tumour progression

Congestive heart failure



What is the most likely diagnosis?

1. Pneumonitis induced by immune checkpoint inhibition
2. COVID-19 pneumonia
3. Bacterial pneumonia
4. Acute exacerbation of COPD
5. Tumor progression



Should this patient undergo a bronchoscopy?

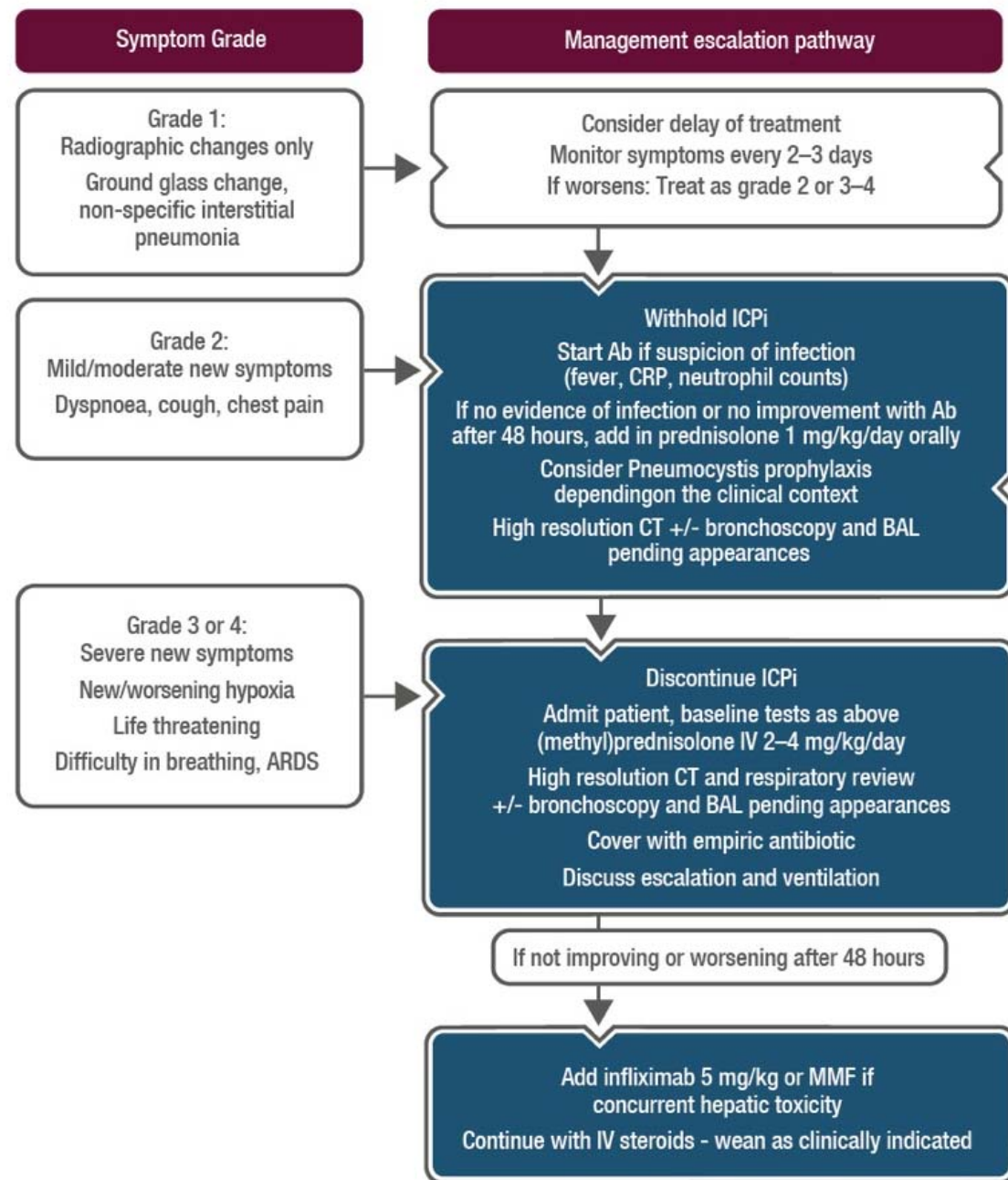
1. Only if clinical deterioration after treatment initiation
2. No, bronchoscopy is contra-indicated in times of COVID-19 because of risk of viral transmission
3. Yes, when SARS-CoV-2 infection cannot be ruled out by initial investigations



Review of work-up of possible ICI-induced pneumonitis



Immune-related pneumonitis: diagnosis of exclusion

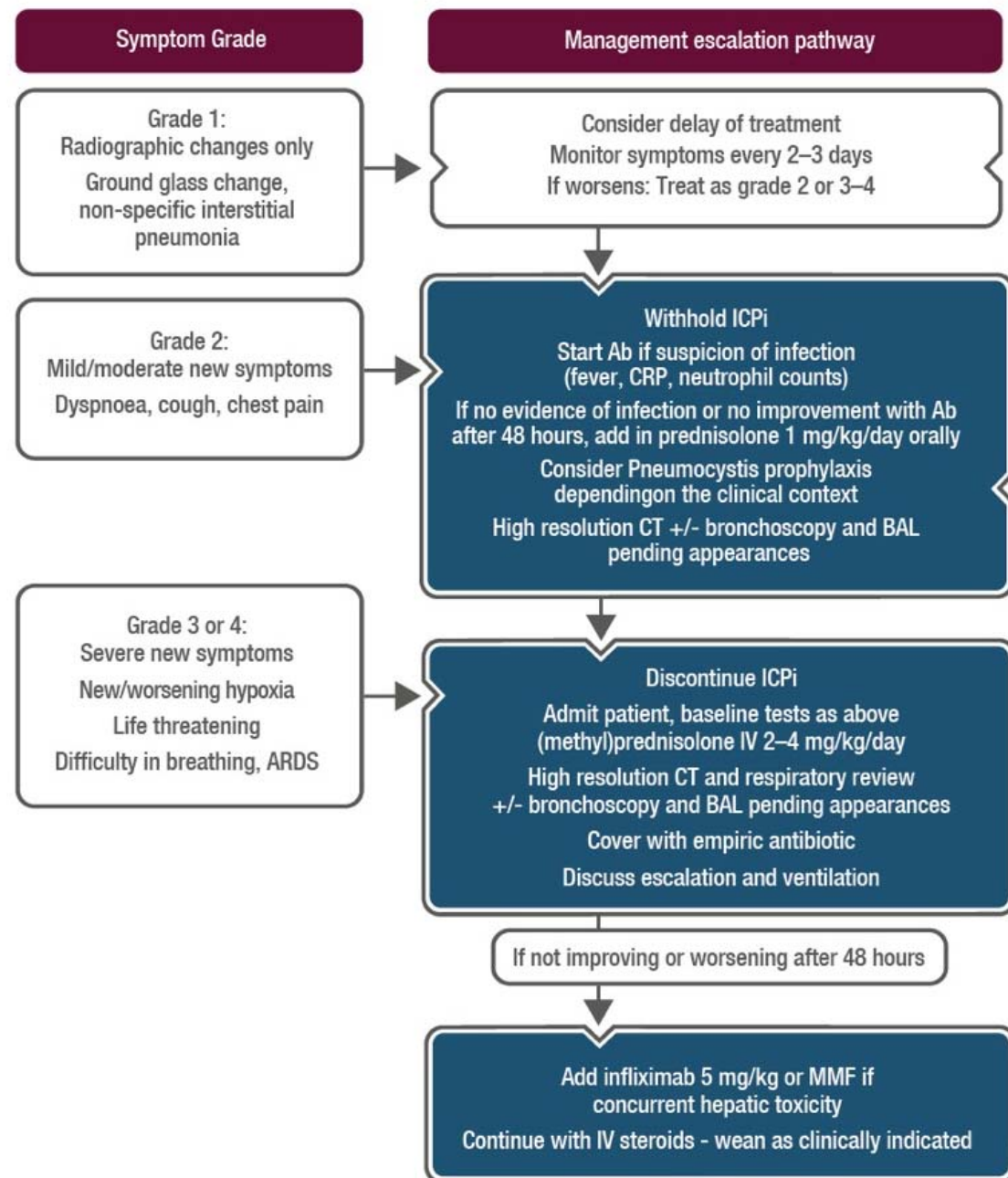


- ▶ Laboratory testing
- ▶ Chest CT imaging
- ▶ Bronchoscopy in symptomatic patients before start of high dose CS

→ Multidisciplinary input involving oncology, pulmonology and radiology recommended



Immune-related pneumonitis: diagnosis of exclusion



- ▶ SARS-CoV-2 RT-PCR on nasopharyngeal swab
- ▶ Laboratory testing
- ▶ Chest CT imaging
- ▶ Bronchoscopy in selected cases

→ Multidisciplinary input involving oncology, pulmonology and radiology recommended

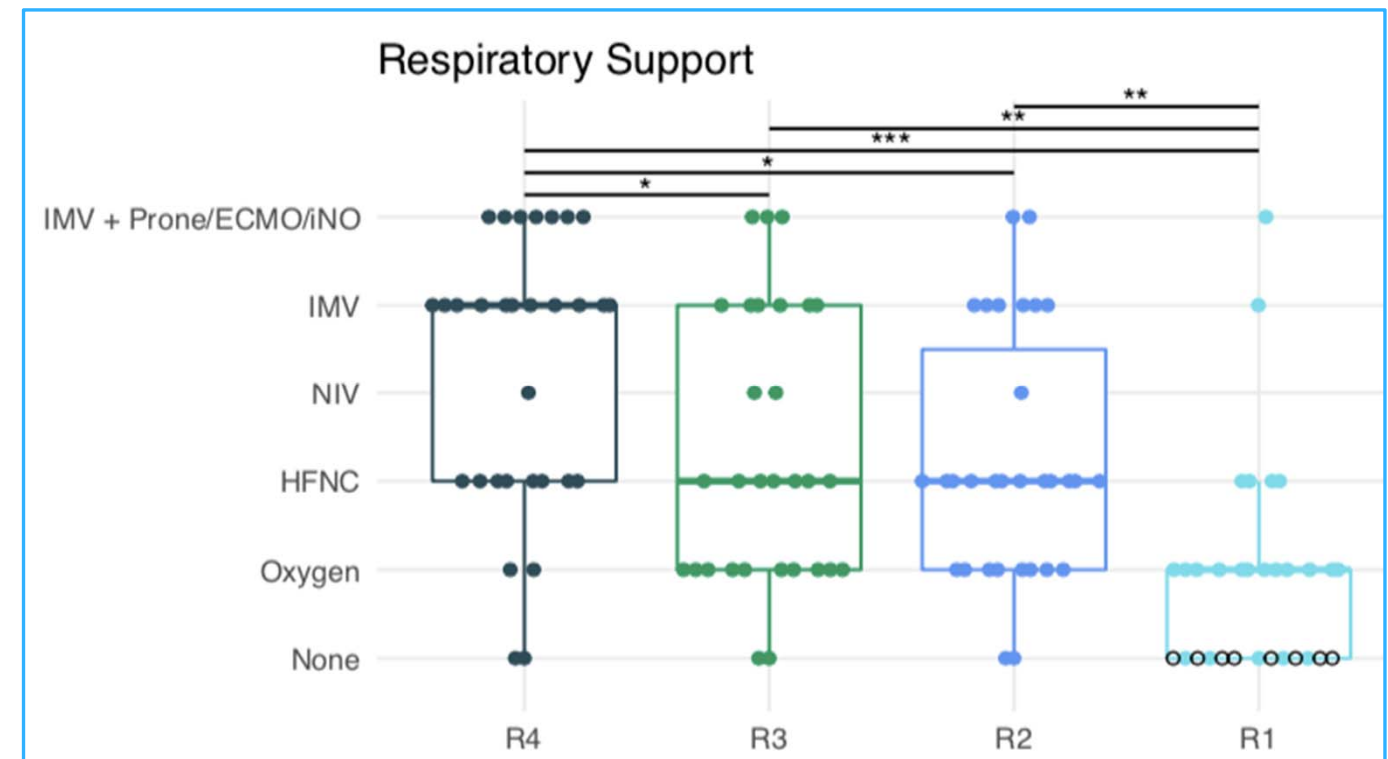
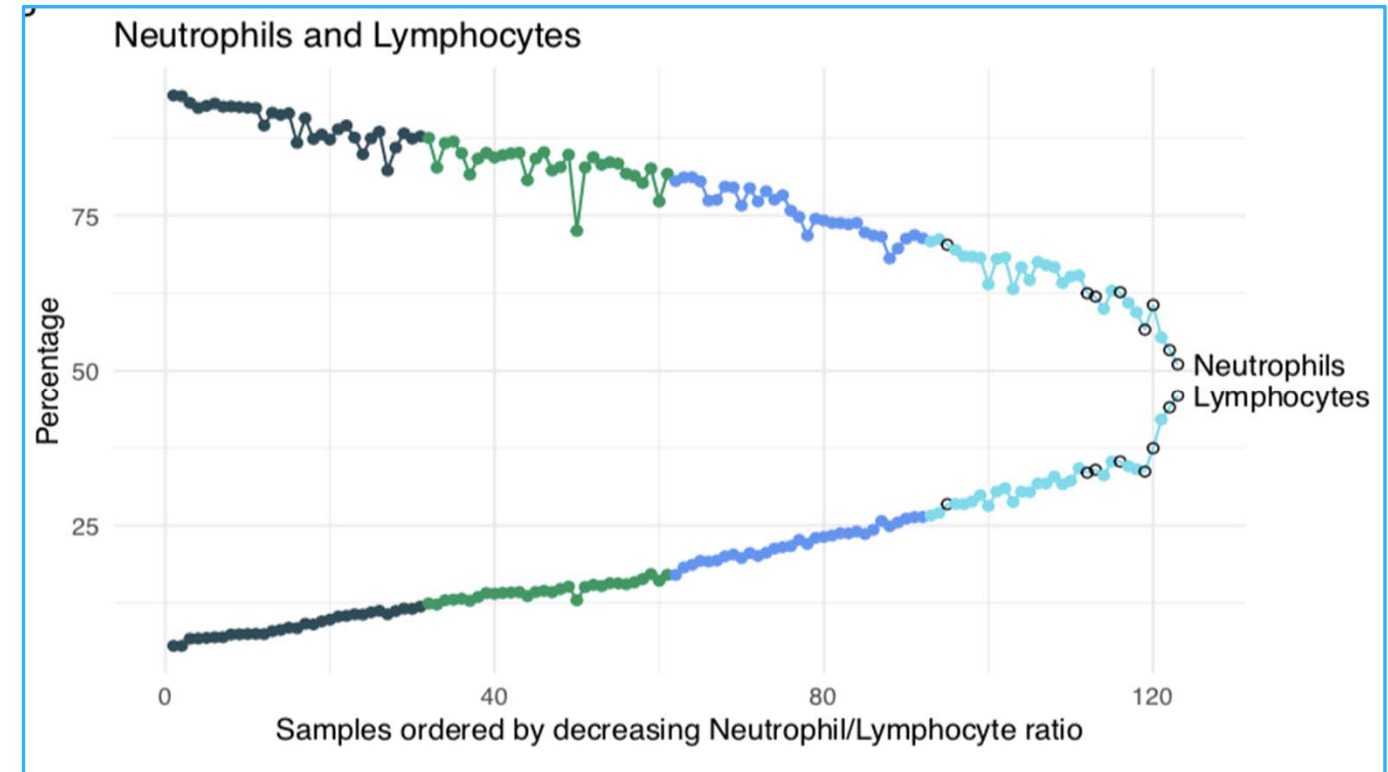


Laboratory findings: non-specific

RT-PCR for SARS-CoV-2 on nasopharyngeal swab:

- Specificity: high
- Sensitivity: moderate

	ICI- pneumonitis	COVID-19 pneumonia
Lymphocyte count	↓ (30%) ↑ (37%)	↓ (83%)
CRP	↑ (91%)	↑ (60%)
D-dimers	?	↑ (46%)
Ferritin	?	↑ in severe disease



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Chest CT findings: non-specific

Moderate to severe features consistent with COVID-19
Any pre-test probability of COVID-19
No significant resource constraints

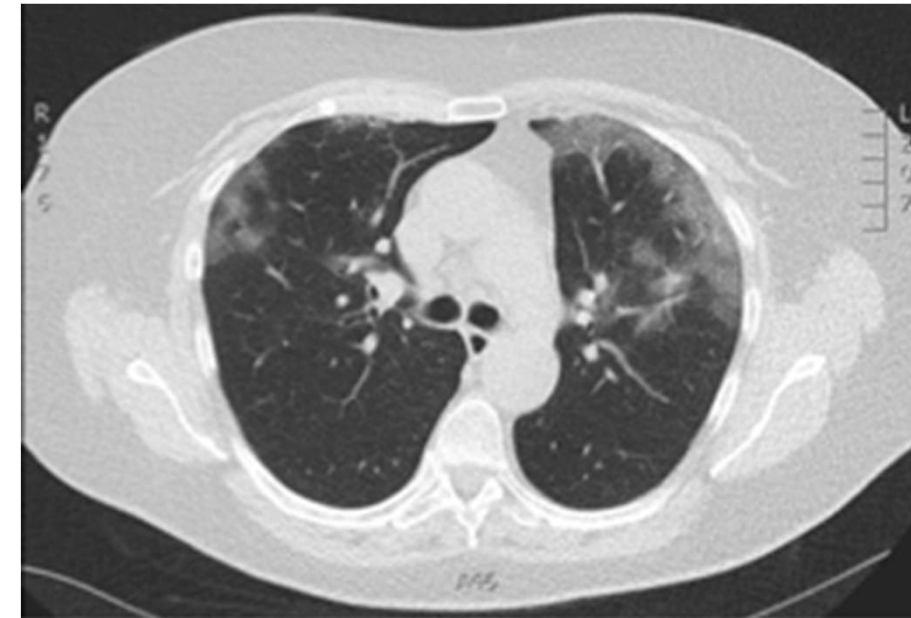
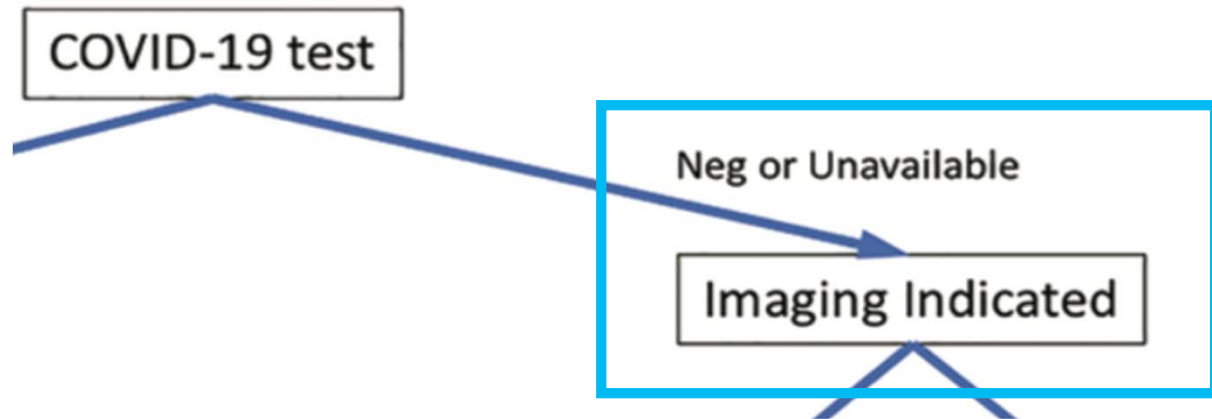


Table 2: Typical Features for Pulmonary Involvement of COVID-19

Obligatory Features
Ground-glass opacities, with or without consolidations, in lung regions close to visceral pleural surfaces, including the fissures (subpleural sparing is allowed) and multifocal bilateral distribution
Confirmatory Patterns
Ground-glass regions
Unsharp demarcation, (half) rounded shape
Sharp demarcation, outlining the shape of multiple adjacent secondary pulmonary lobules
Crazy paving
Patterns compatible with organizing pneumonia
Thickened vessels within parenchymal abnormalities found in all confirmatory patterns



Chest CT findings: non-specific

Moderate to severe features consistent with COVID-19
 Any pre-test probability of COVID-19
 No significant resource constraints

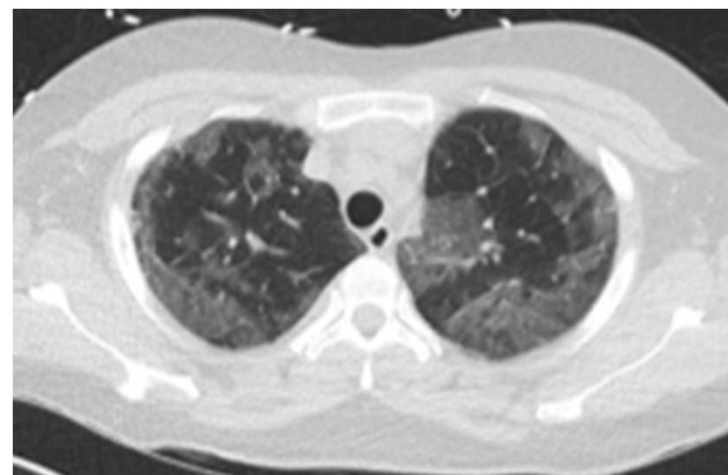
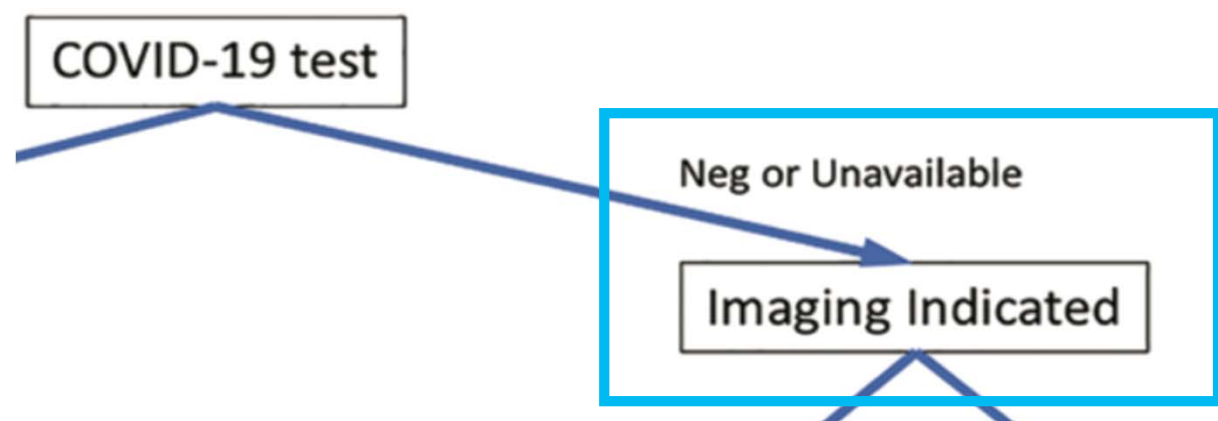


Table 2: Uncommon CT Findings in Isolated COVID-19 Pneumonia

CT Finding and Study	No. of Patients in Study	No. of Patients with Finding
Unilateral distribution		
Bai et al (17)	219	41 (19)
Meng et al (18)	58	34 (59)
Chen et al (19)	145	27 (19)
Central distribution		
Zhao et al (11)	101	1 (1)
Han et al (15)	108	2 (2)
Bai et al (17)	219	3 (1)
Nodules		
Zhao et al (11)	101	23 (23)
Bai et al (17)	219	70 (32)
Li and Xia (20)	51	11 (22)
Crazy-paving pattern		
Chung et al (21)	21	4 (19)
Bernheim et al (16)	121	6 (5)
Bai et al (17)	219	11 (5)
Reverse halo sign		
Bernheim et al (16)	121	2 (2)
Bai et al (17)	219	11 (5)
Li and Xia (20)	51	2 (4)

Note.—Numbers in parentheses are percentages. COVID-19 = coronavirus disease 2019.

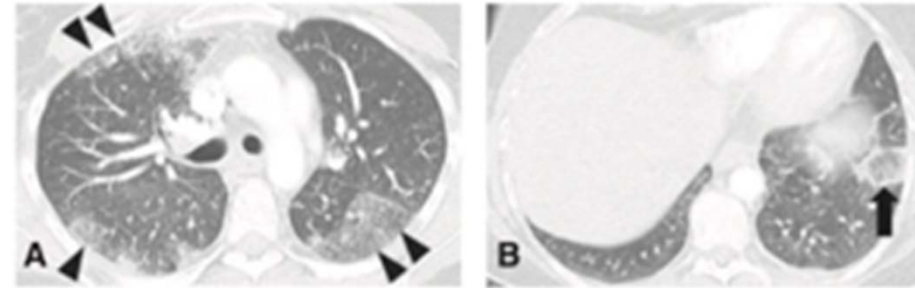
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Chest CT findings: non-specific

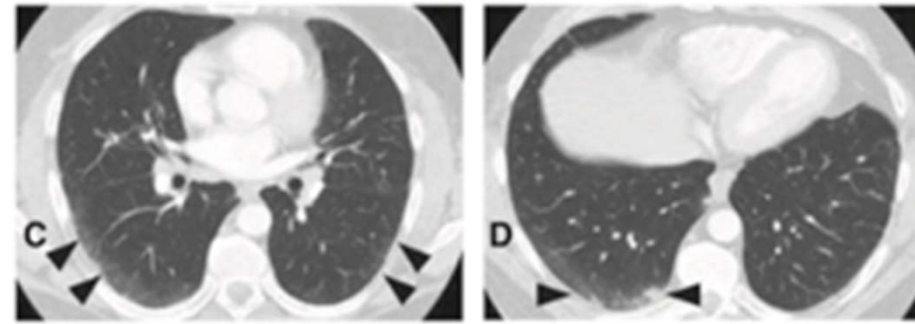
ICI-pneumonitis CT patterns

OP
(+/- 65%)



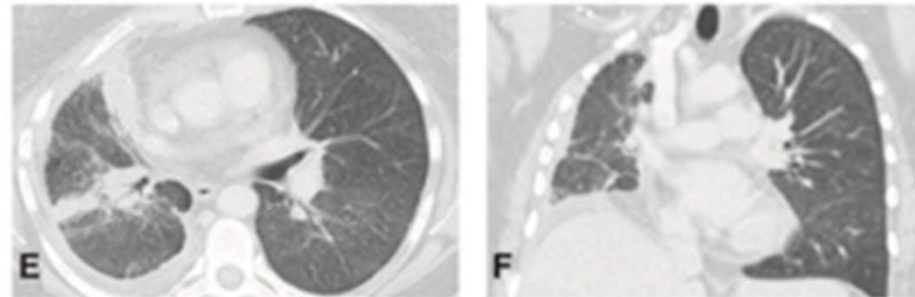
Bilateral patchy opacities with peripheral or peribronchovascular predominance, mainly middle/lower lung. Can be combined with GGOs & nodules.

NSIP
(+/- 15%)



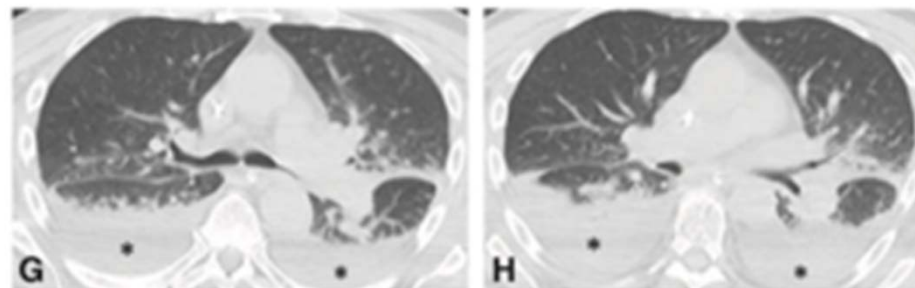
GGOs and sub-pleural reticulation with a lower zone predominance and usually fairly symmetric.

HP
(+/- 10%)



Diffuse GGOS and ill-defined centrilobular nodules in both lungs.

AIP/ARDS
(+/- 10%)



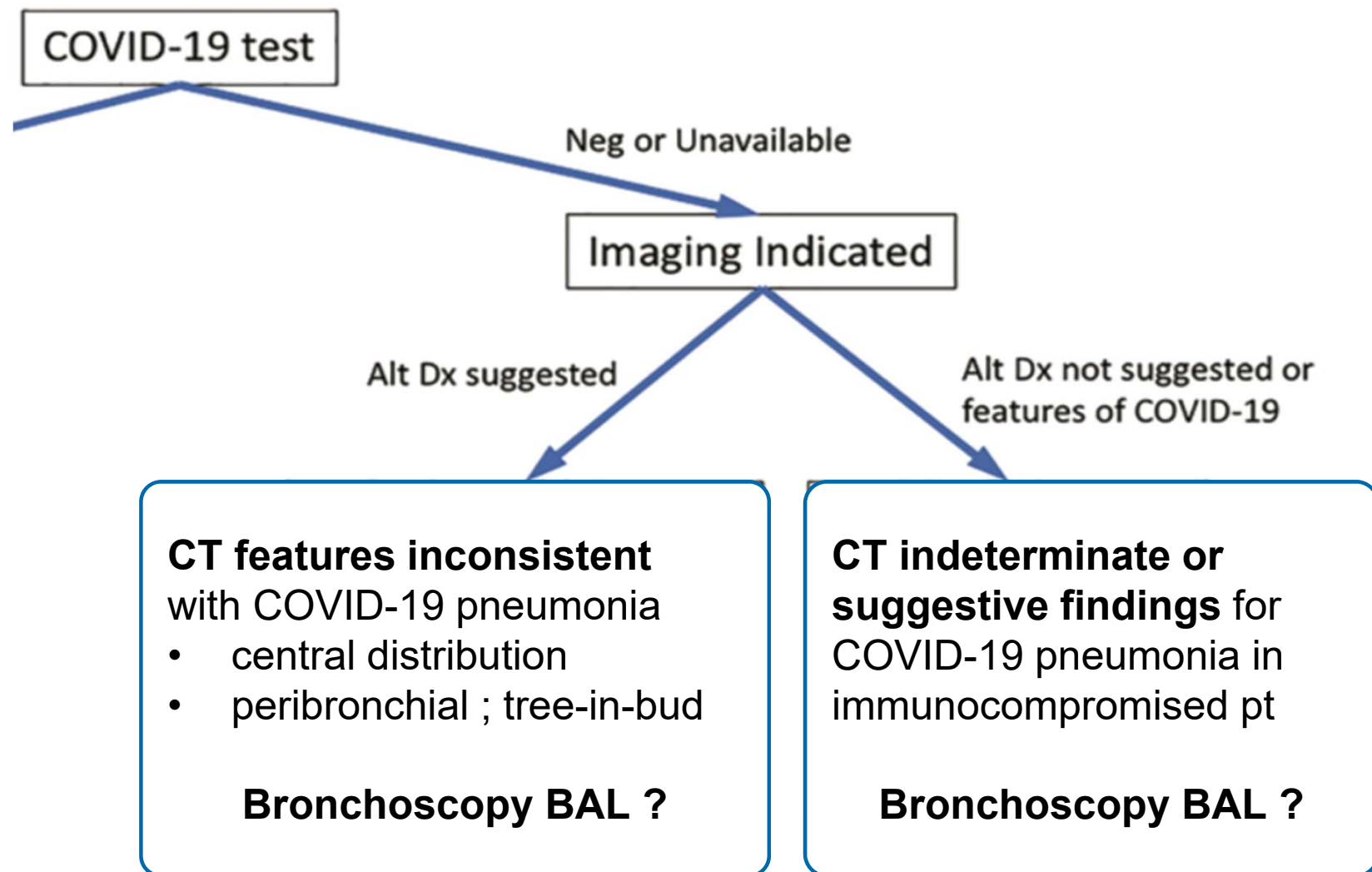
Diffuse GGO or consolidative opacities involving majority of the lungs. Interlobular septal thickening & crazy-paving patterns can be seen.

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Role for bronchoscopy?

Moderate to severe features consistent with COVID-19
Any pre-test probability of COVID-19
No significant resource constraints



CAVE

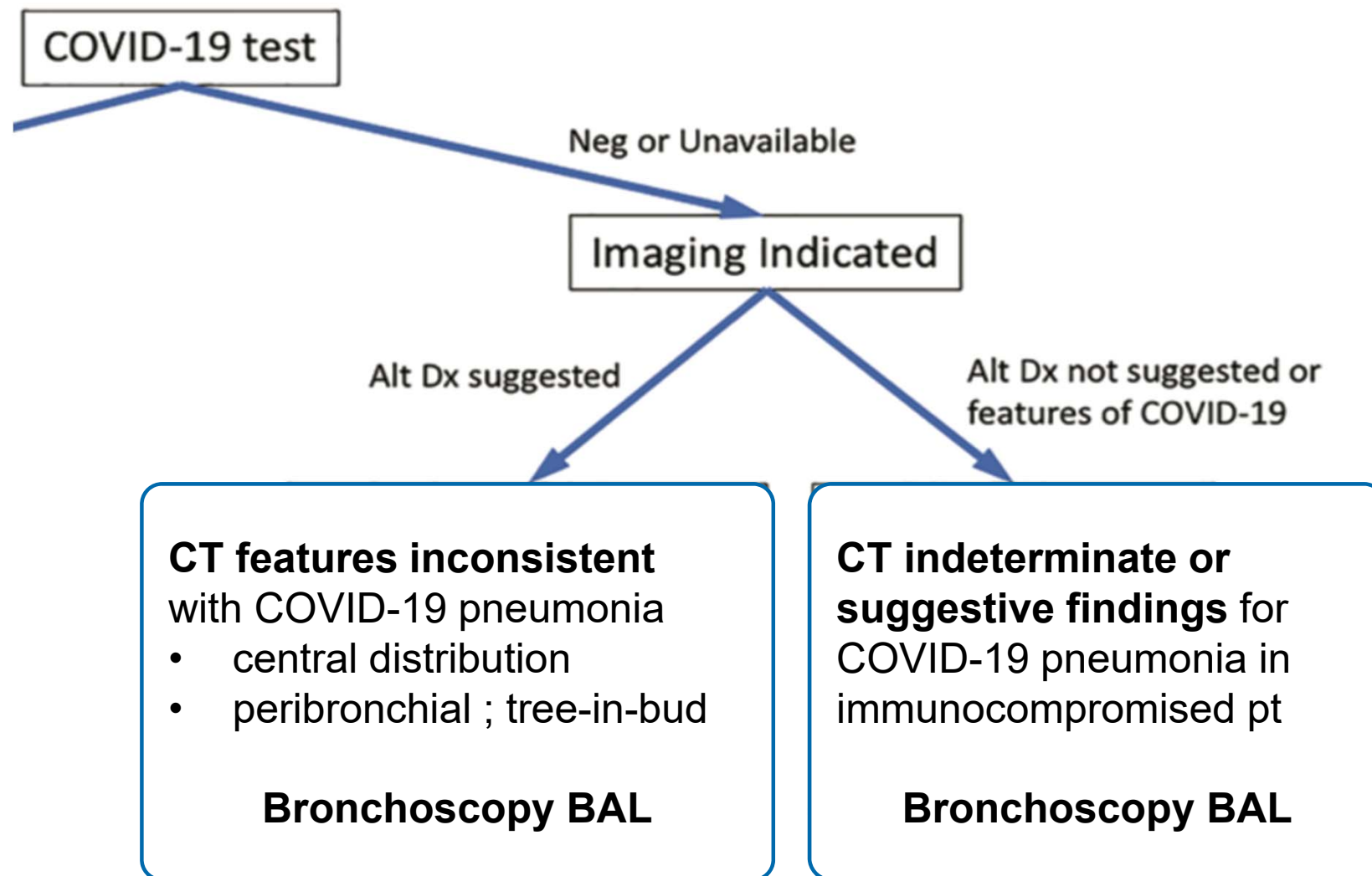
- ▶ Risk of transmission to caregiver
- ▶ Risk of respiratory collapse of patient

(contra-indication in unstable patient: RR>20/min, or HR>120/’ or O2 sat <93% with ≥5L O2/’)



Role for bronchoscopy

Moderate to severe features consistent with COVID-19
Any pre-test probability of COVID-19
No significant resource constraints

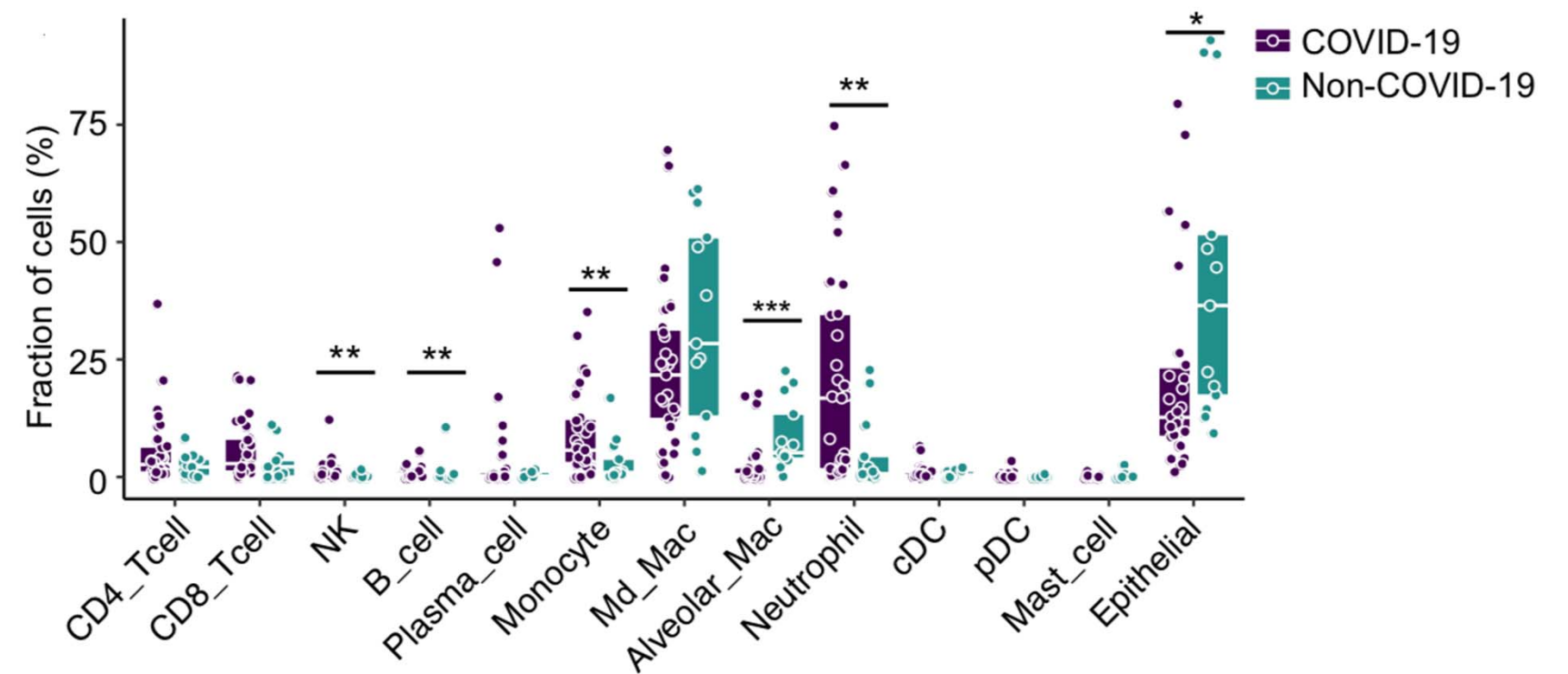
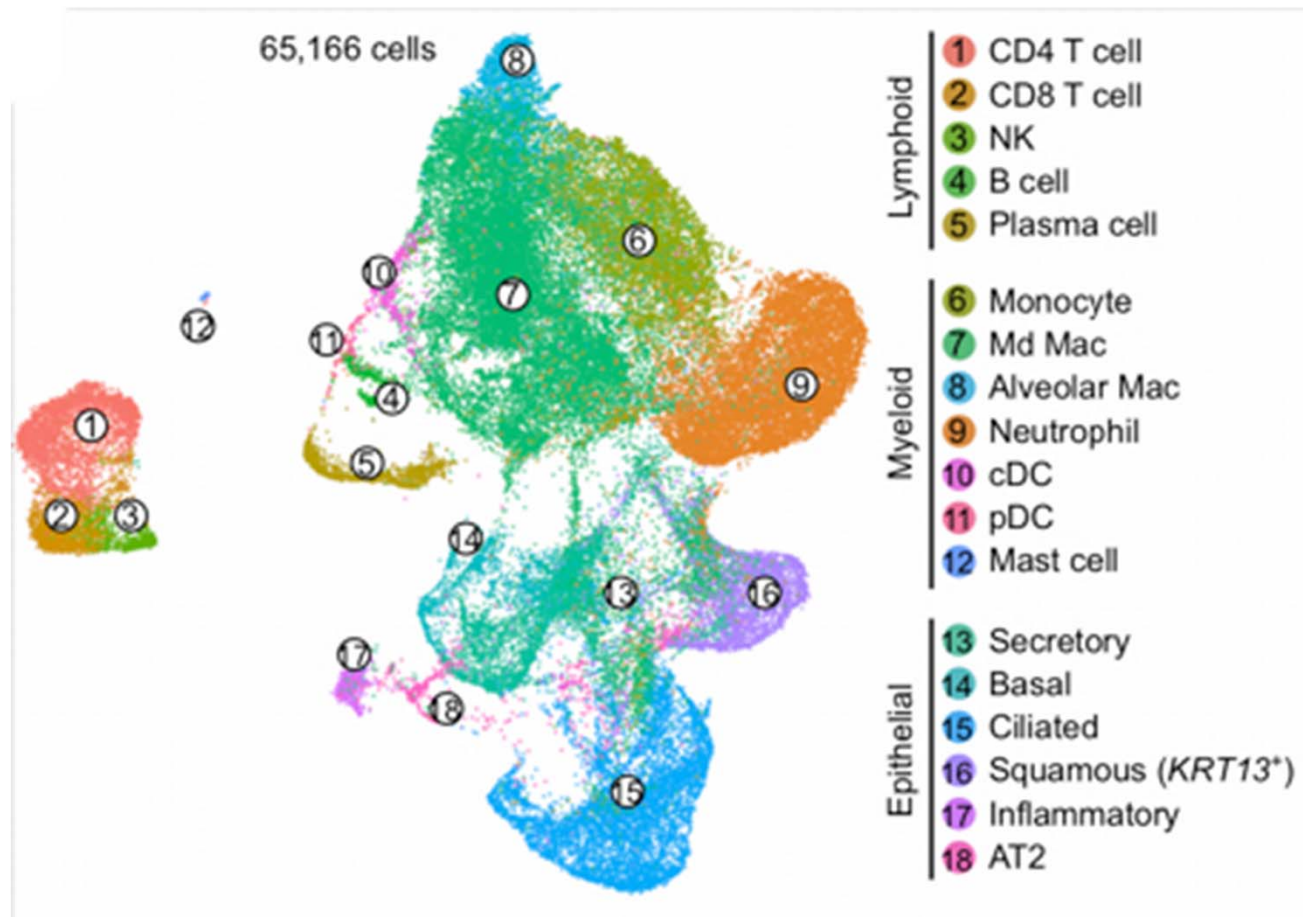


Pro

- ▶ SARS-CoV-2 PCR BALF:
 - highest sensitivity (93%)
- ▶ Allows assessing alternative diagnoses



Immune cell count BALF as a diagnostic clue?



- **Neutrophils:** markedly higher in COVID-19 (35%) than in non-COVID pneumonia (10%) or ICI-P (depleted)
- **Lymphocytes:** higher in ICI-P (37%) than in healthy BALF and COVID-19 (11%)



Patient history



History: since 4 days:
Fever (38.7°C)
Lethargy
Progressive dyspnea
Productive cough

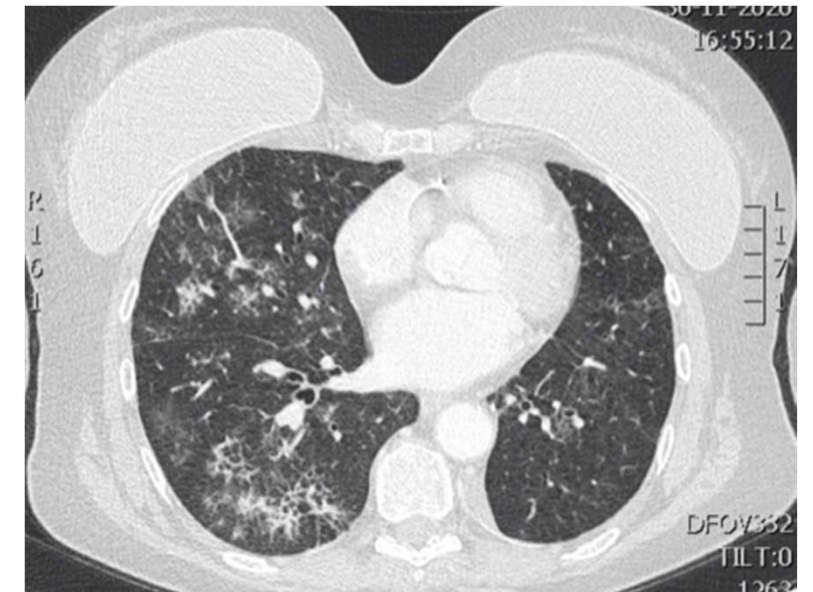


Clinical examination
HD stable, 38.2°C, sat.88%
Generally ill appearance
Bilateral ronchi and crackles



Laboratory results

Lymphopenia $800 \times 10^6/l$
CRP 52mg/l
D-Dimers $952 \mu g/l$
SARS-CoV-2 PCR negative
(nasopharyngeal swab)



SARS-CoV-2 PCR BALF
positive



Case study



Treatment

4l/min supplemental oxygen

Ceftriaxone 2g 1x/d (5d)

Methylprednisolone 40mg 1x/d (5d)

Enoxaparin 40mg 1x/d

No antiviral therapy



Conclusion

- ▶ Discriminating ICI-induced pneumonitis from COVID-19 is essential, as delayed or incorrect treatment increases the risk of a severe disease course
- ▶ Beware of asymptomatic COVID-19 mimicking G1 ICI-induced pneumonitis
 - advisable to temporarily withhold ICI
- ▶ Bronchoscopy + BAL has a place in the work-up of ICI-pneumonitis
 - only in clinically stable patients & with full safety measures for caregivers in place:
 - to exclude alternative diagnoses
 - if clinical suspicion of COVID-19 is high and nasopharyngeal swab negative



Thank you for your kind attention



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