Vascular morphology of Alveolar Capillary Dysplasia revisited: report of a case, literature review and a morphometric approach to assess cases of atypical clinical presentation

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atypical clinical presentation = late onset (5-28 weeks) = longer survival (12-250 weeks)

SOFFOET September 2018

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Original Article

Histopathologic features of alveolar capillary dysplasia with misalignment of pulmonary veins with atypical clinical presentation ☆,☆☆

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Histopathologic and Genetic Features of Alveolar Capillary Dysplasia with Atypical Late Presentation and Prolonged Survival

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2019

Quantitative analysis of capillary morphology in Alveolar Capillary Dysplasia (ACD): a pilot study on two cases and an age-matched control

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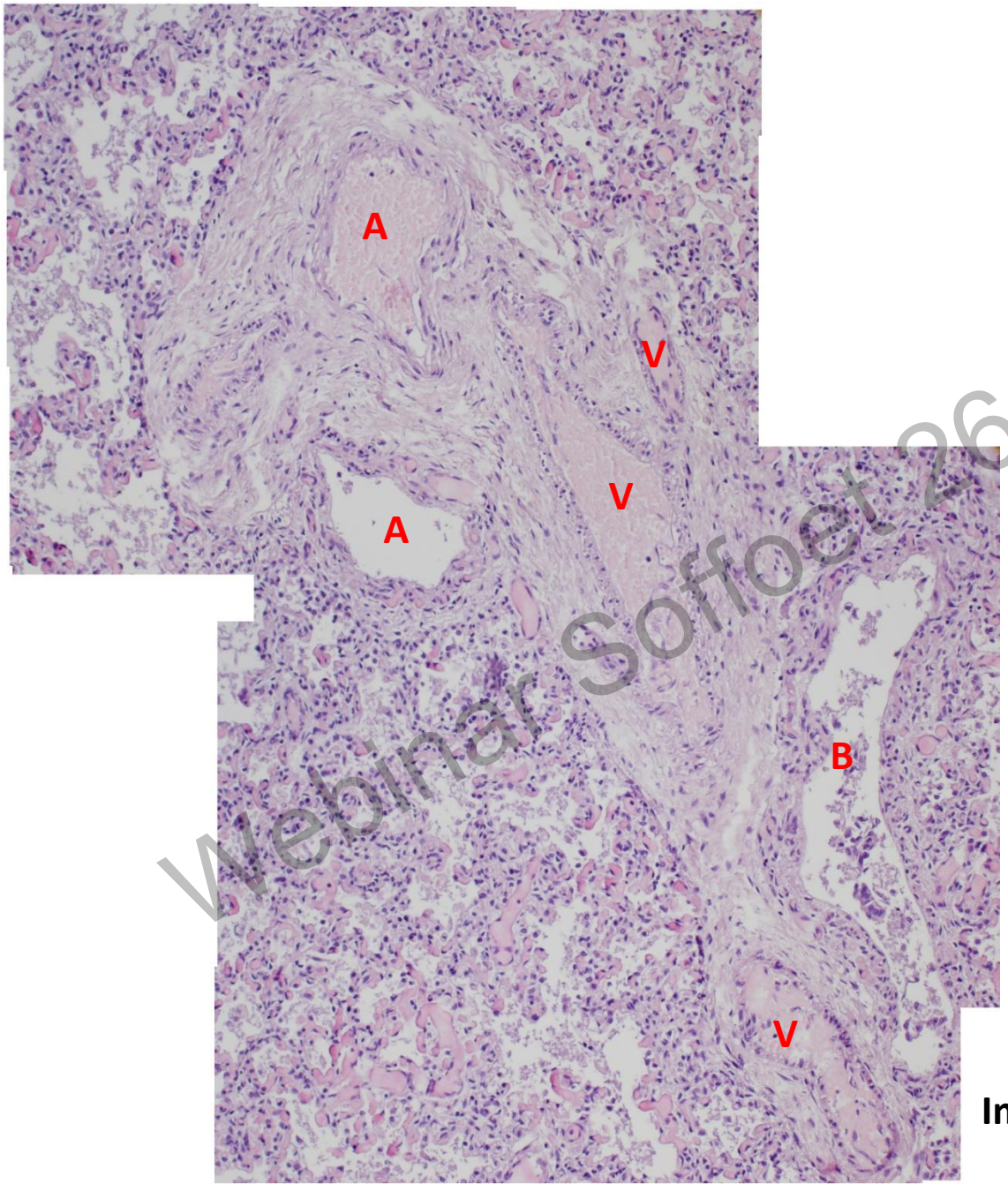
SOFFOET March 2021

Main histopathological features

- large abnormal veins accompany arteries and bronchi *(aka misaligned pulmonary veins)*
- loose thickened mesenchyme in the interstitium
- muscularization of alveolar walls arterioles and hypertrophy of media of small arteries
- capillaries not in contact with alveoli (blood-air barrier reduction)
- reduced number of capillaries

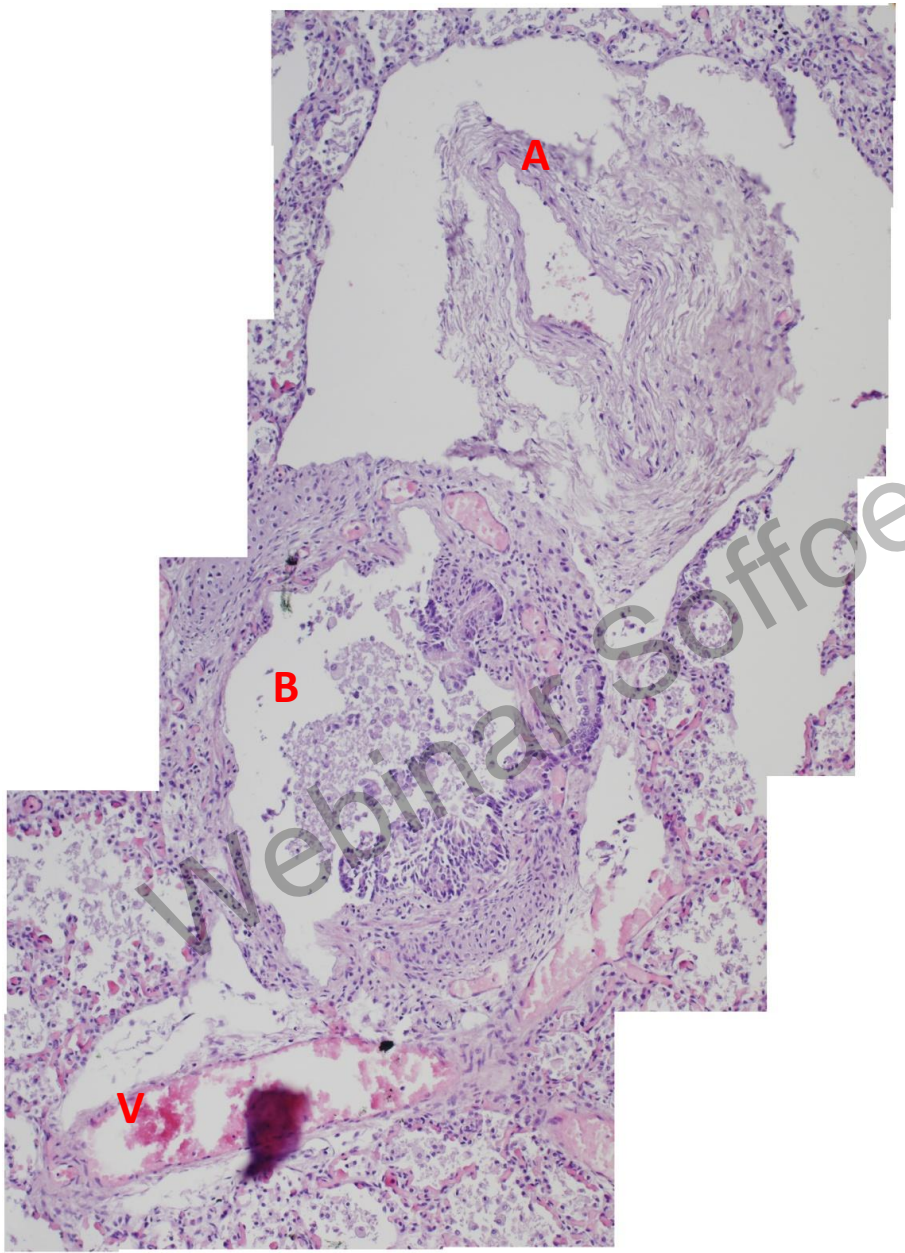
Abnormally situated vein accompanies artery and bronchiole (1)



- A = artery
- B = bronchiole
- V = vein

Image mosaic x 10

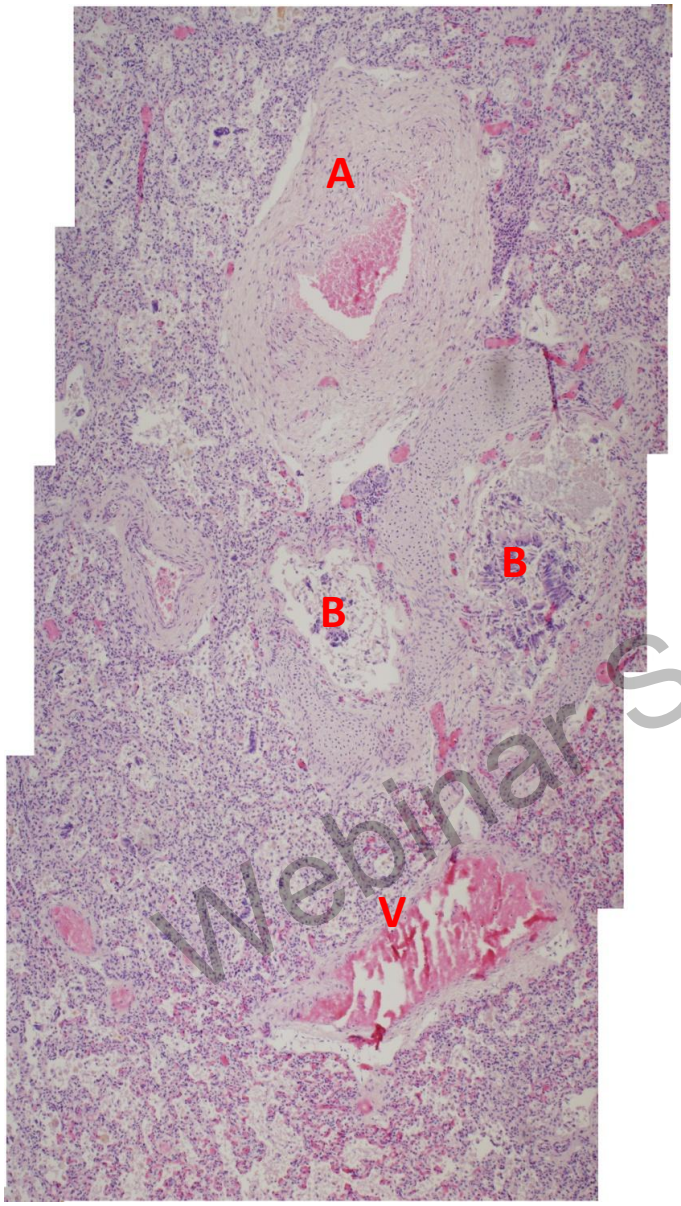
Abnormally situated vein accompanies artery and bronchiole (2)



- A = artery
- B = bronchiole
- V = vein

Image mosaic x 10

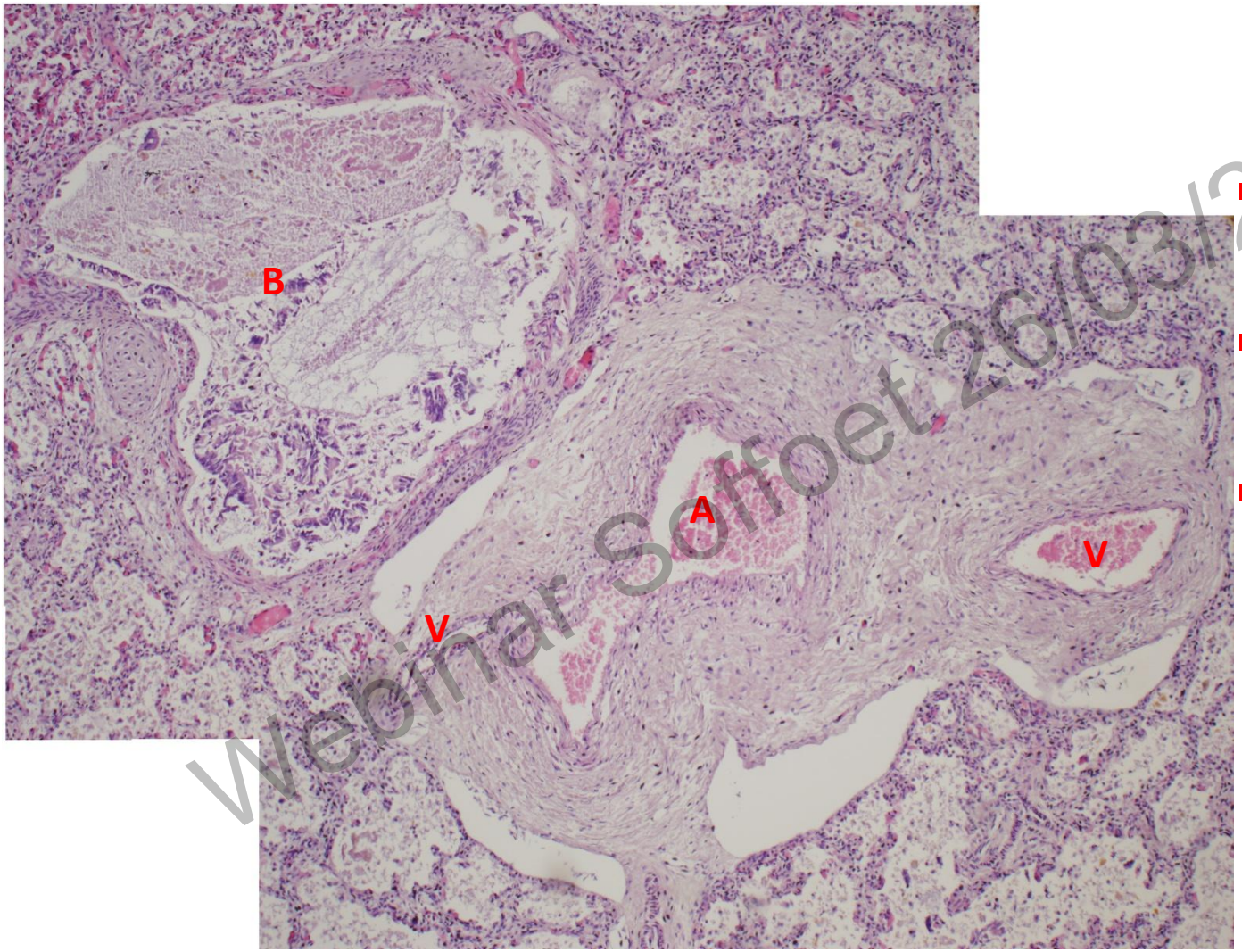
Abnormally situated vein accompanies artery and bronchiole (3)



- A = artery
- B = bronchiole
- V = vein

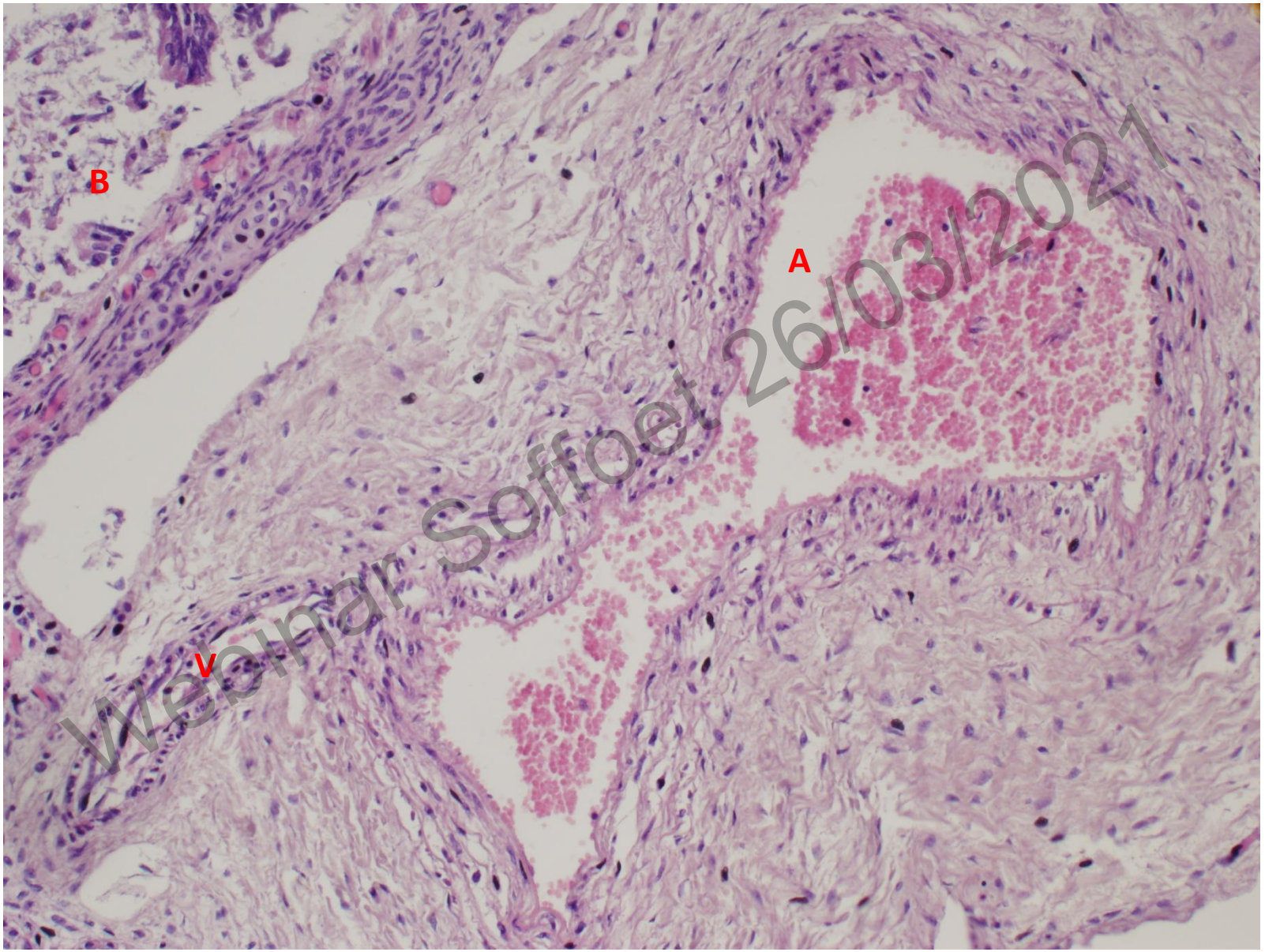
Image mosaic x 10

Abnormally situated vein accompanies artery and bronchiole (4)

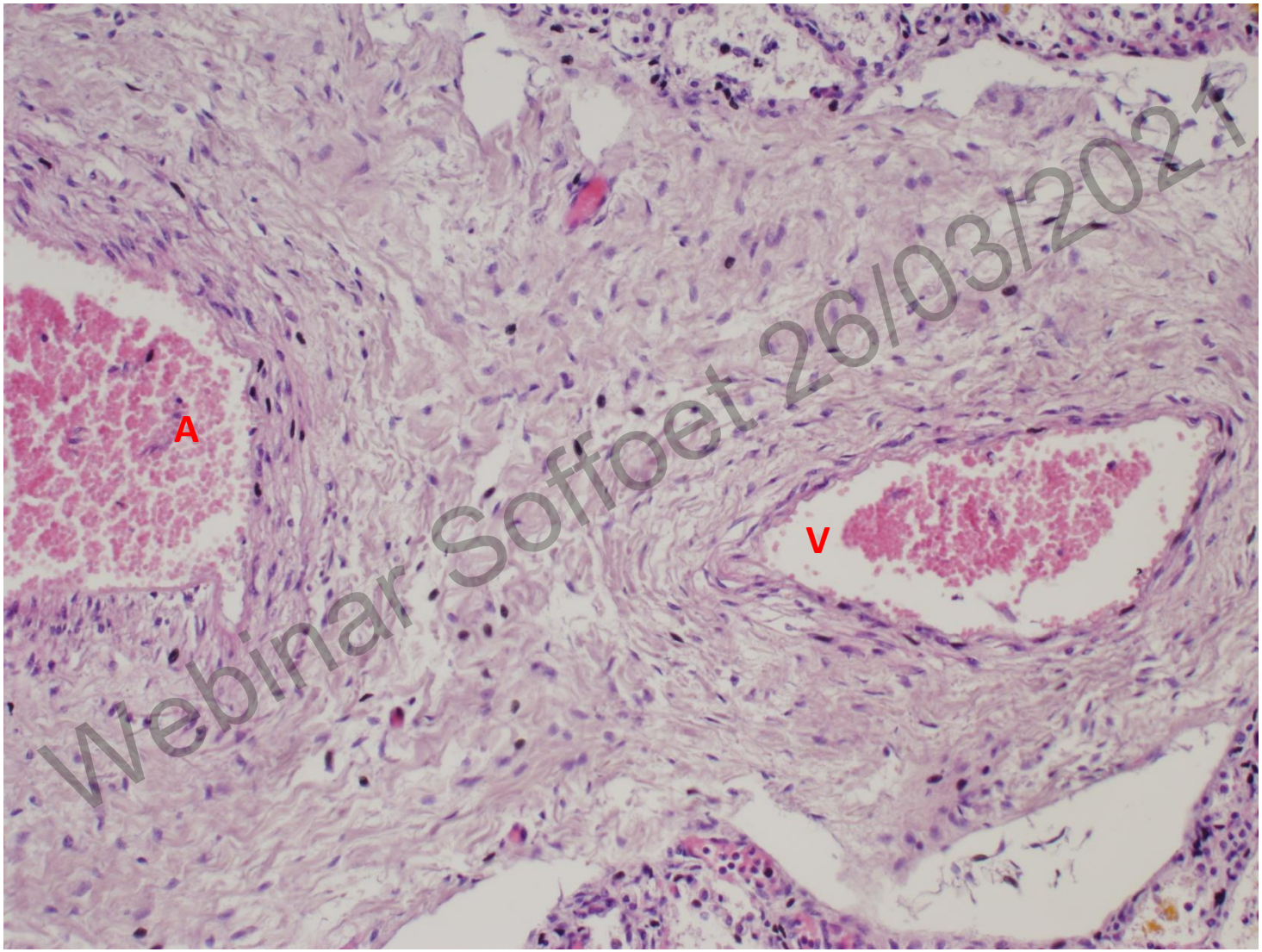


- A = artery
- B = bronchiole
- V = vein

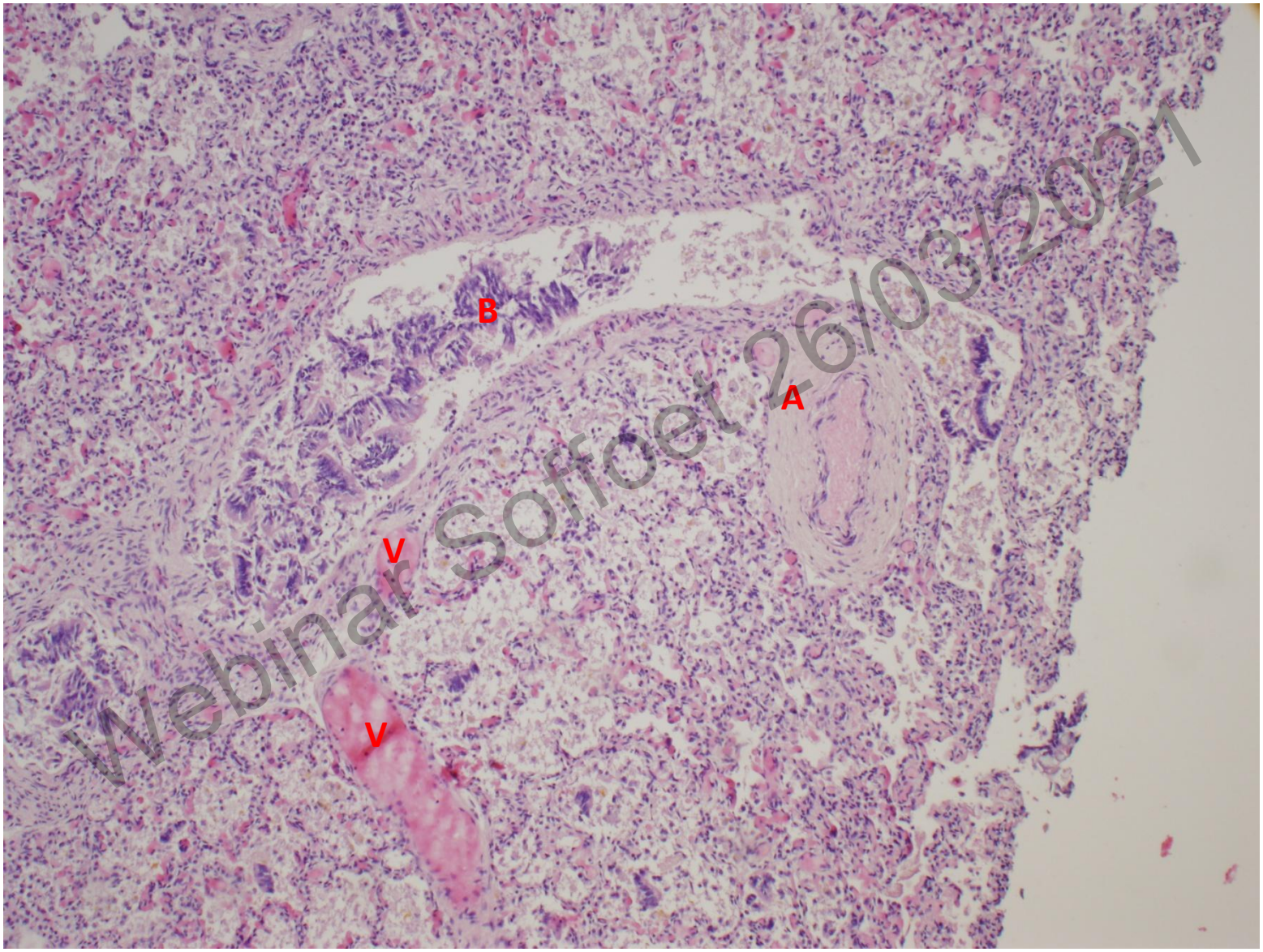
Abnormally situated vein accompanies artery and bronchiole (4): detail



Abnormally situated vein accompanies artery and bronchiole (4): detail

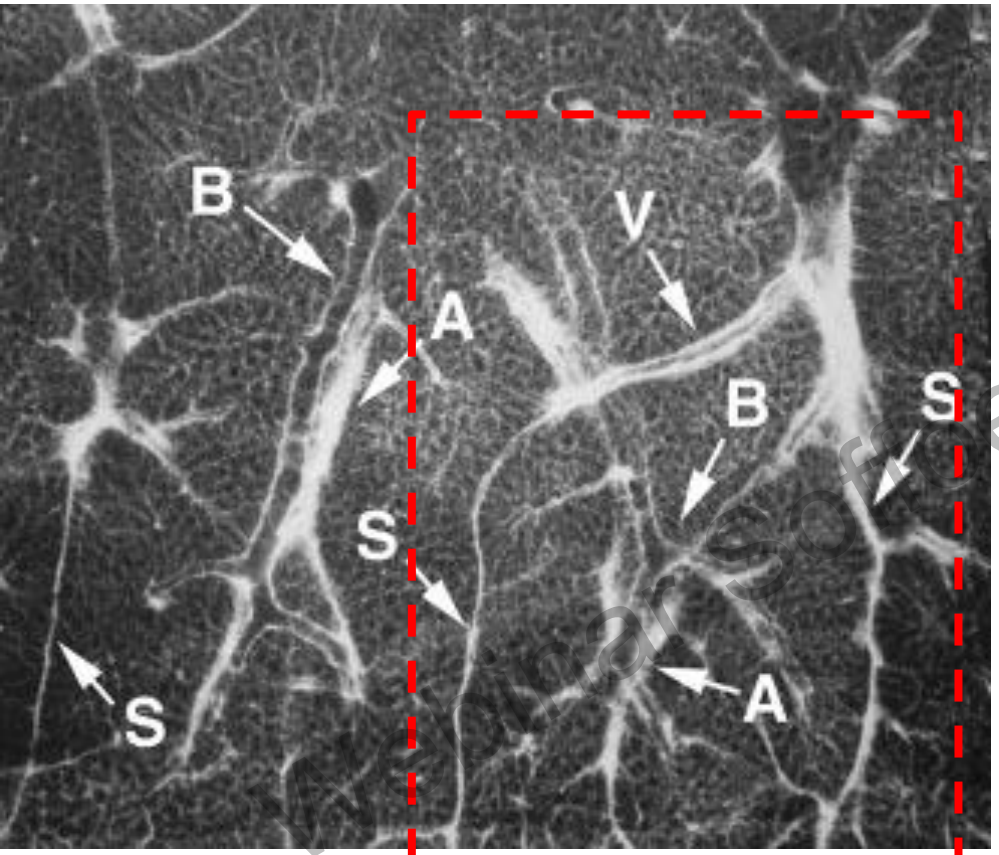


Abnormally situated vein accompanies artery and bronchiole (5)



CT: secondary pulmonary lobule

Webb WR. Thin-Section CT of the Secondary Pulmonary Lobule: Anatomy and the Image. The 2004 Fleischner Lecture. *Radiology 2006; 239: 322-38.*

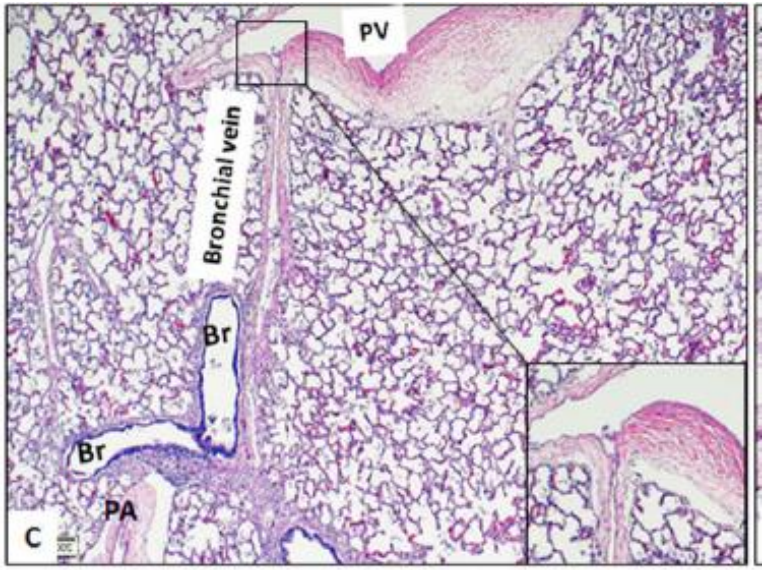


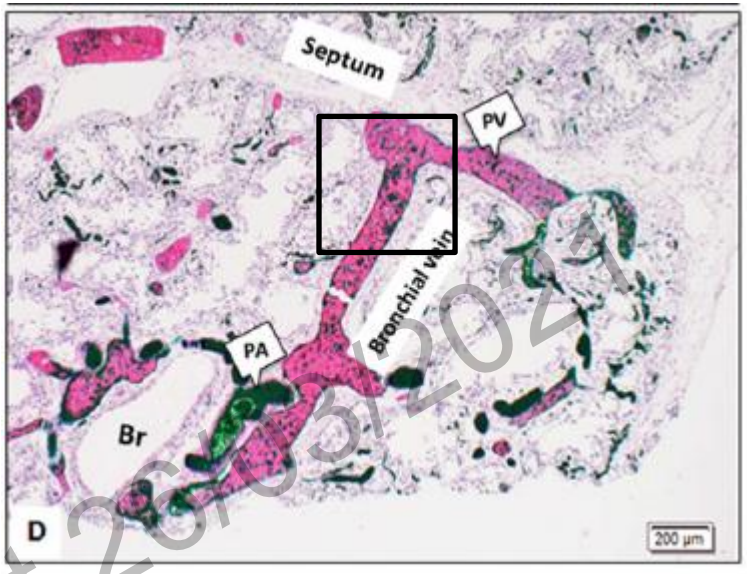
- B = bronchiole
- A = arteriole
- V = vein
- S = septum

bronchiole + arteriole
in central position

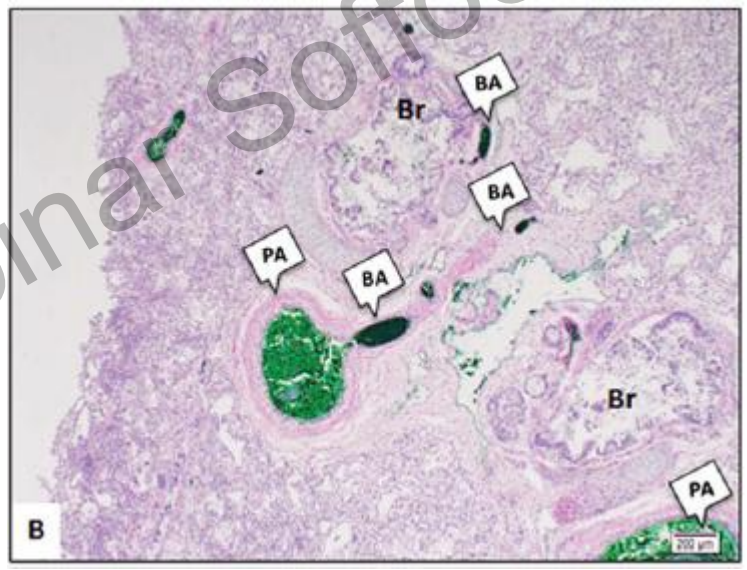
vein
in delimiting septa

Shunts (1): bronchial vein pulmonary vein





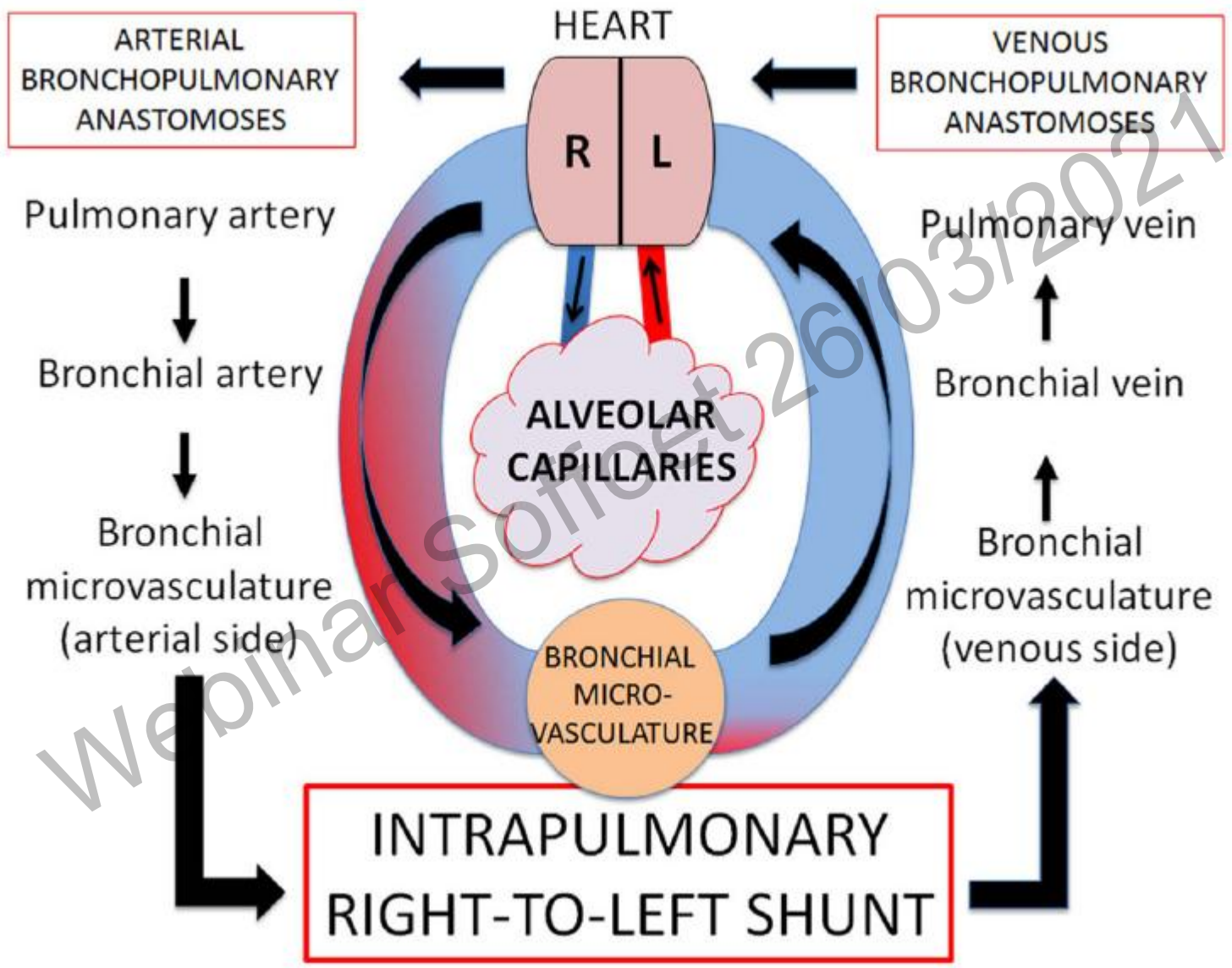
Shunts (2): bronchial artery pulmonary artery



Galambos et al. Thorax. 2015;70:84-5.

Galambos et al. J Pediatr. 2014;164:192-5.

Shunts (2): general scheme



Galambos et al. Thorax. 2015;70:84-5.

A terminology shift

Alveolar Capillary Dysplasia Associated With Misalignment of Pulmonary Veins (ACDM-MPV)

Popler et al. CHEST 2012; 142: 774–80

Alveolar Capillary–Congenital Acinar Dysplasia (ACD–CAD) spectrum due to a dysmaturation of the fetal pulmonary vasculature

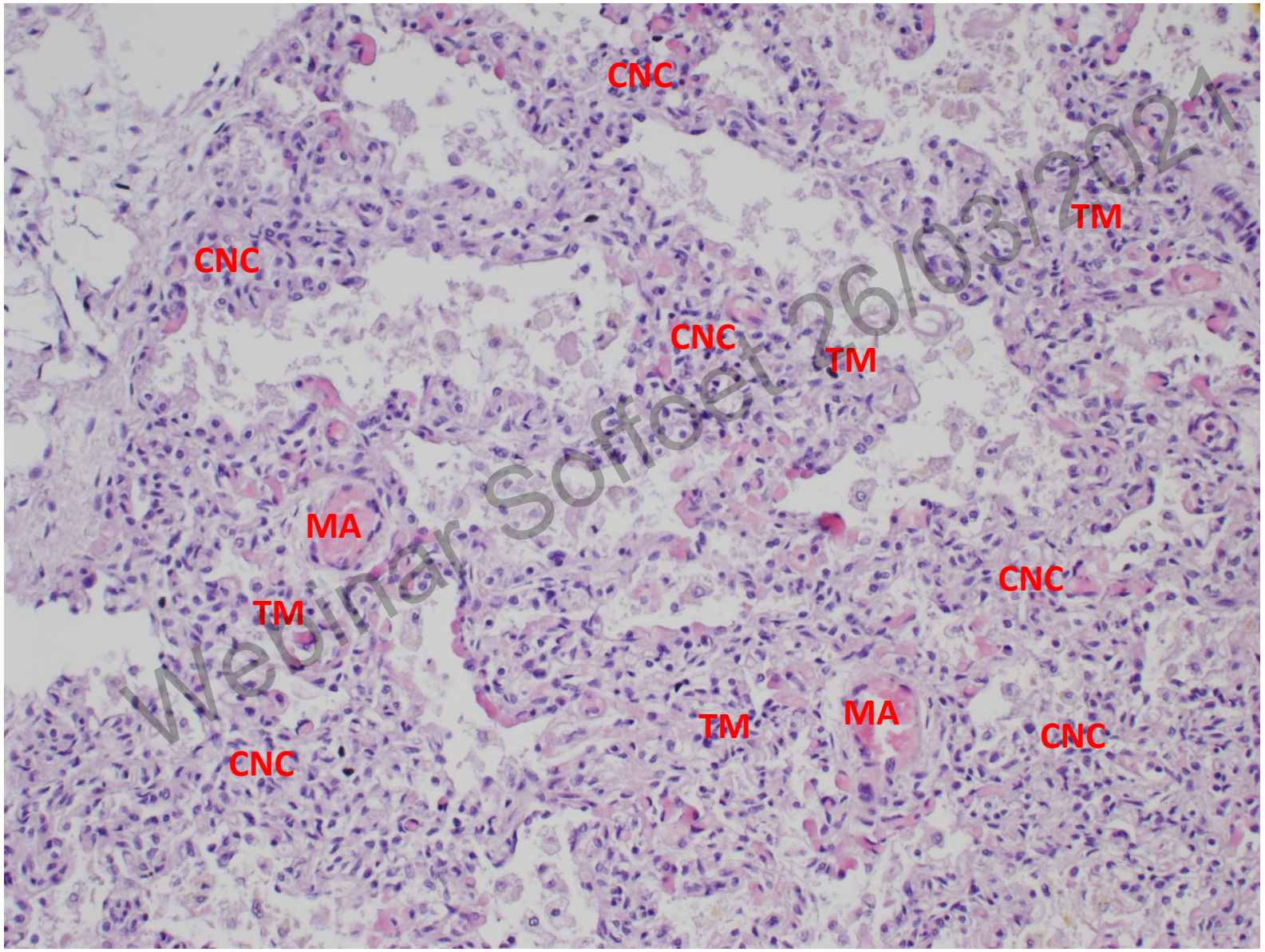
Bush et al. Paediatric Respiratory Reviews 2019; 30: 65–71
Edwards et al. J Pediatr. 2019; 210: 214–219

The so-called misaligned pulmonary veins have been shown to be dilated bronchial veins by detailed morphometric reconstructions

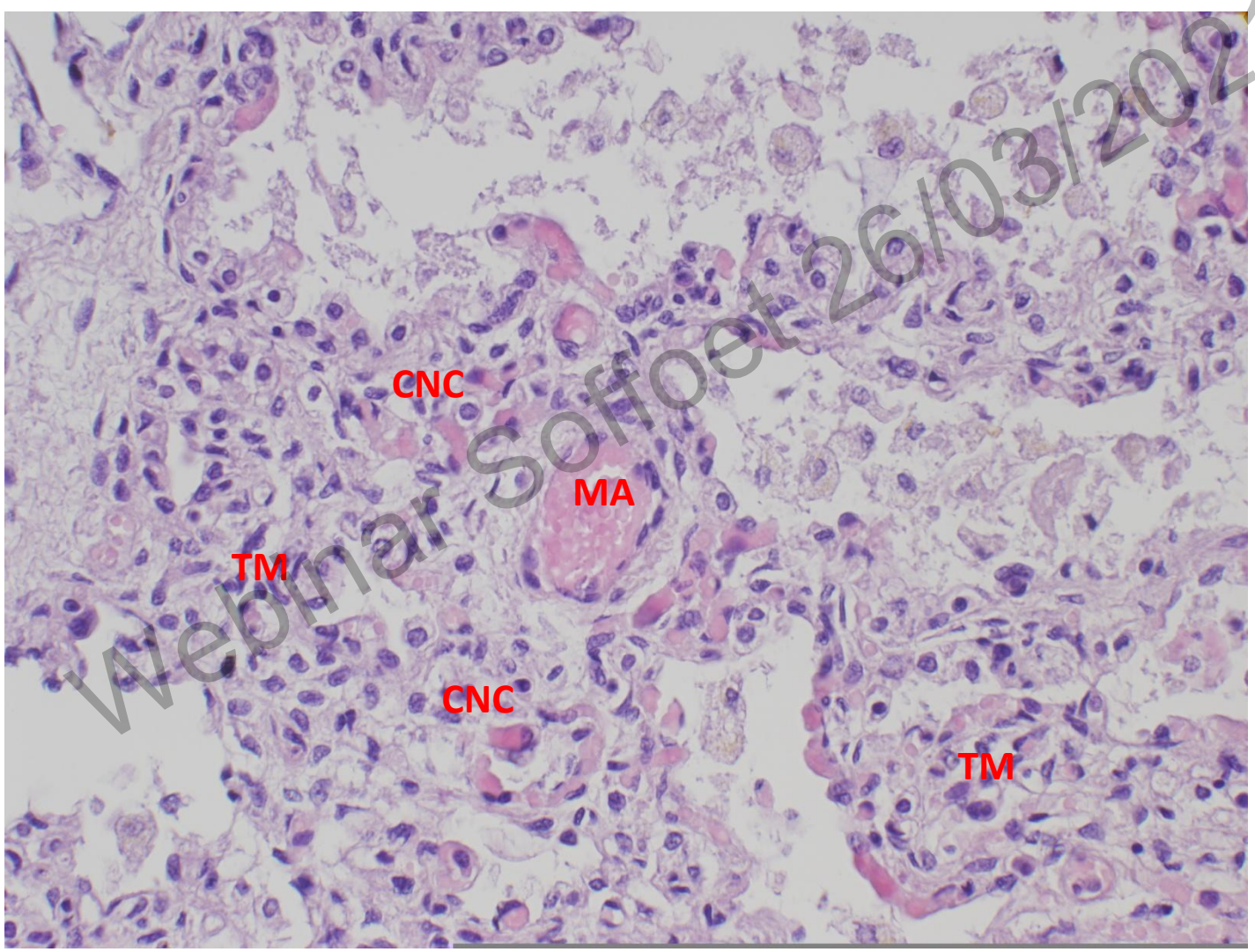
Main histopathological features

- large abnormal veins accompany arteries and bronchi *(aka misaligned pulmonary veins)*
- loose thickened mesenchyme in the interstitium
- muscularization of alveolar walls arterioles and hypertrophy of media of small arteries
- capillaries not in contact with alveoli (blood-air barrier reduction)
- reduced number of capillaries

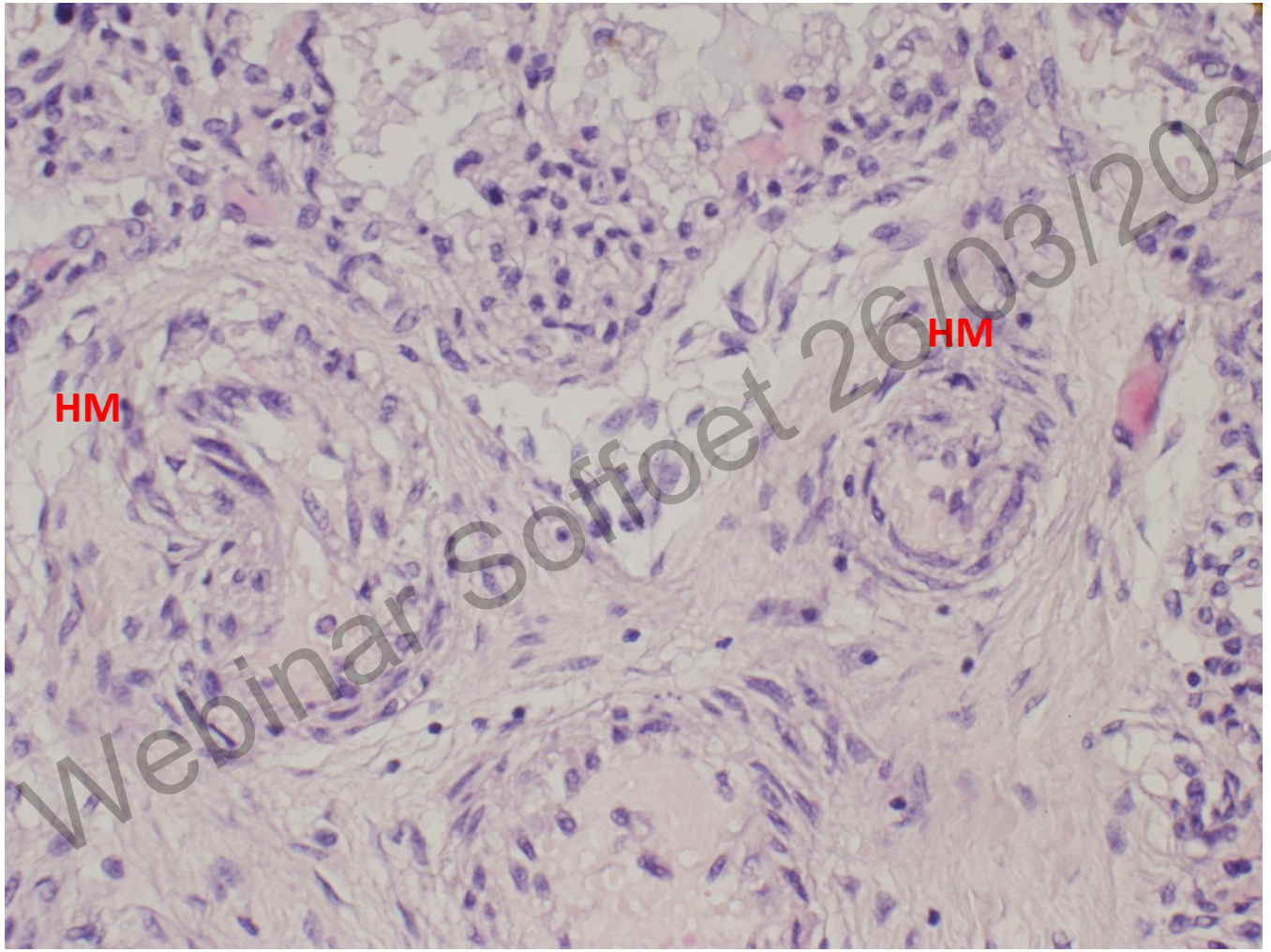
Thickened mesenchyme (TM) in alveolar walls, muscularized arterioles (MA), capillaries not in contact with alveoli (CNC) (1)



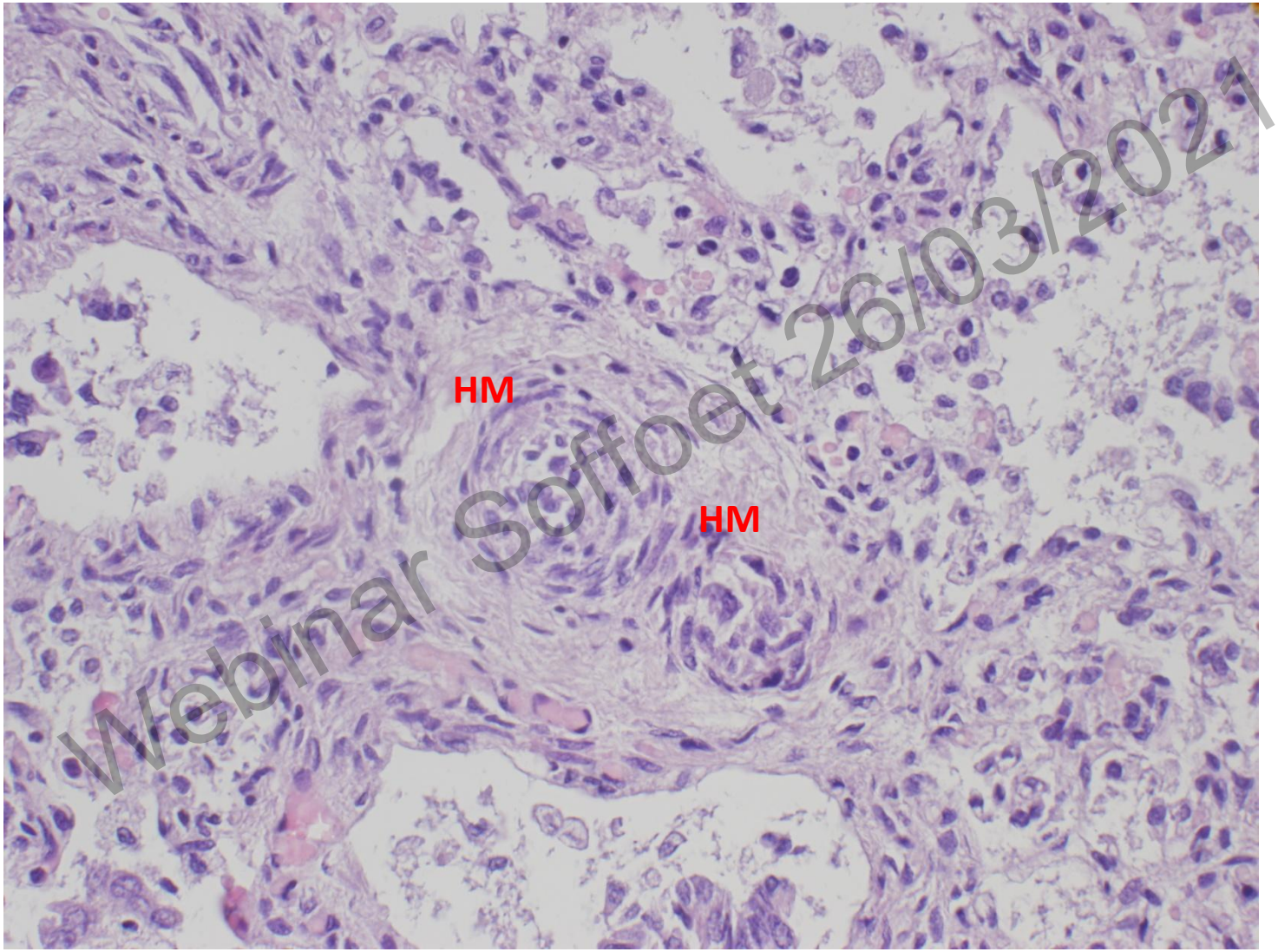
Thickened mesenchyme (TM) in alveolar walls, muscularized arteriole (MA), capillaries not in contact with alveoli (CNC) (2)



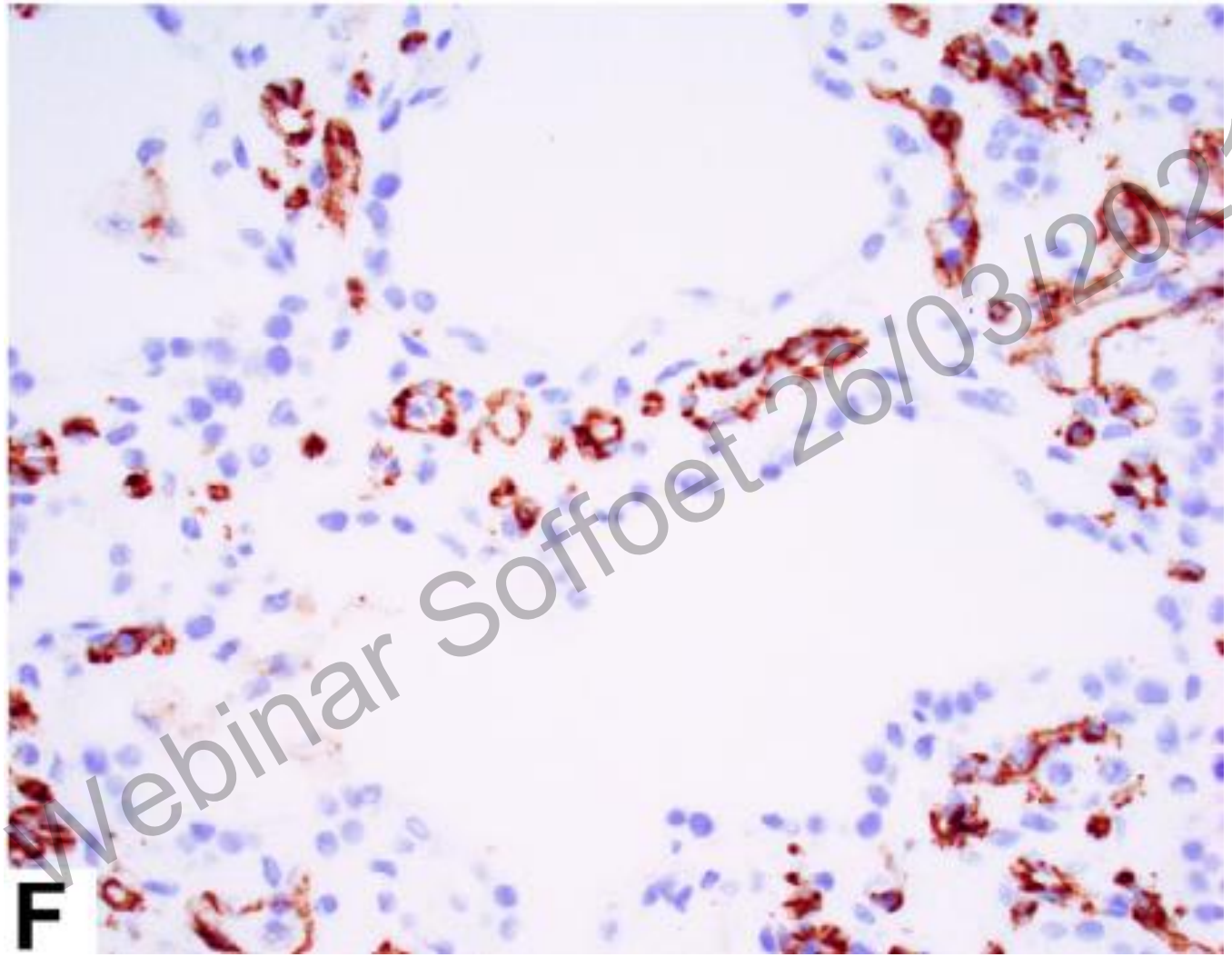
Hypertrophy of media of small arteries (HM) (1)



Hypertrophy of media of small arteries (HM) (2)

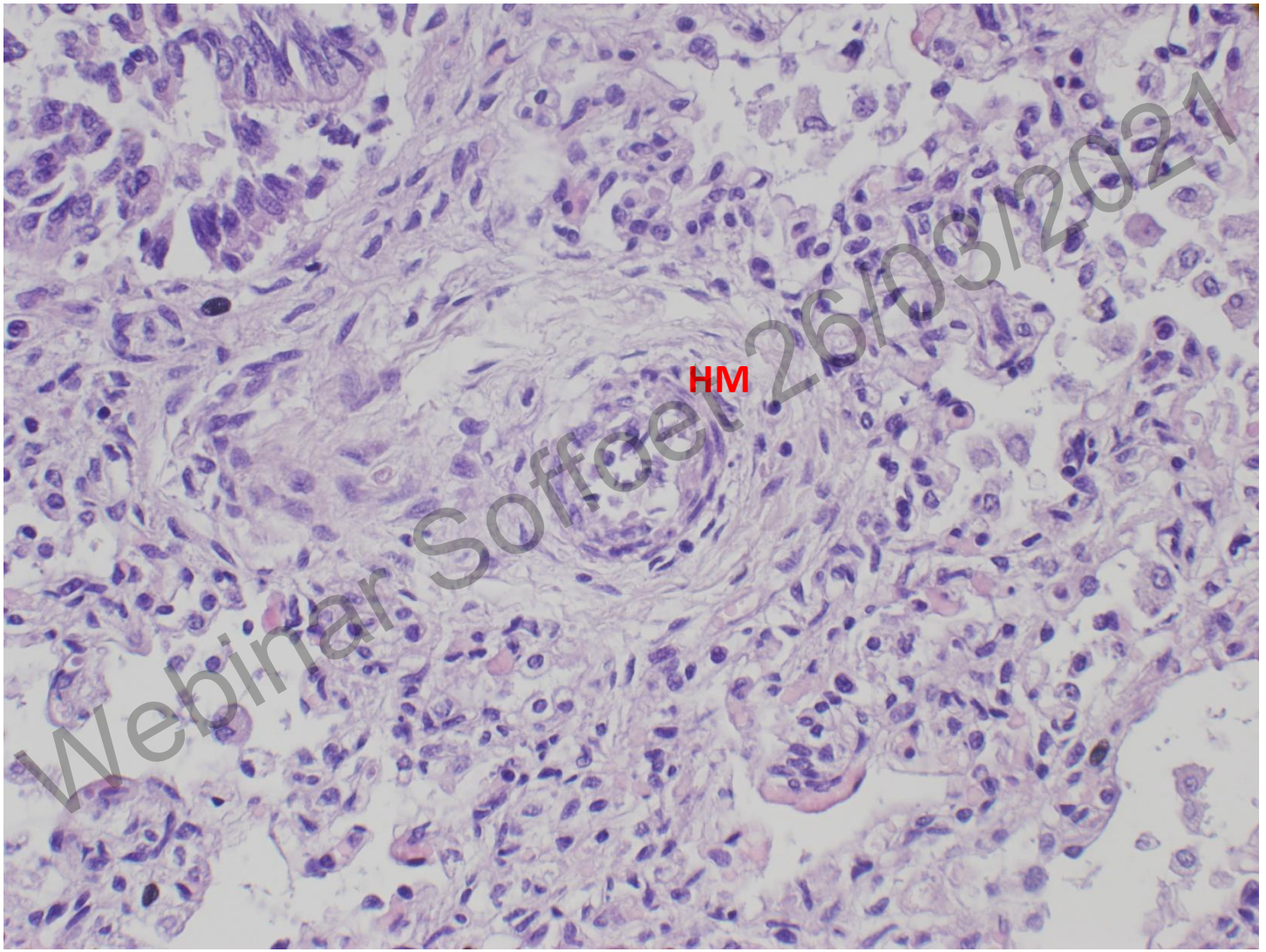


CD31 ACD patient

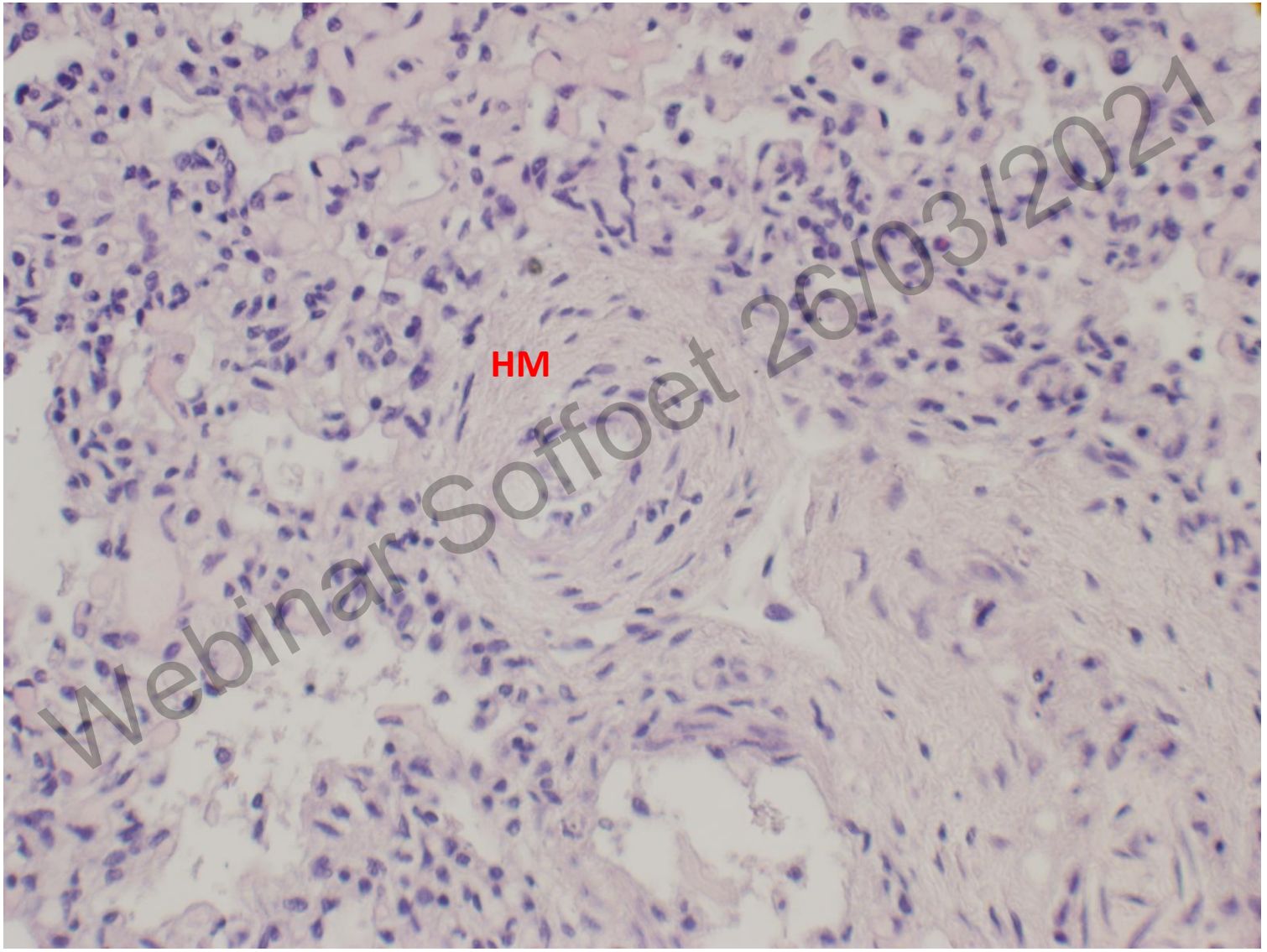


Alturkustani et al. Cardiovasc Pathol. 2021; 50: 107289.

Hypertrophy of media of small arteries (HM) (3)



Hypertrophy of media of small arteries (HM) (3)



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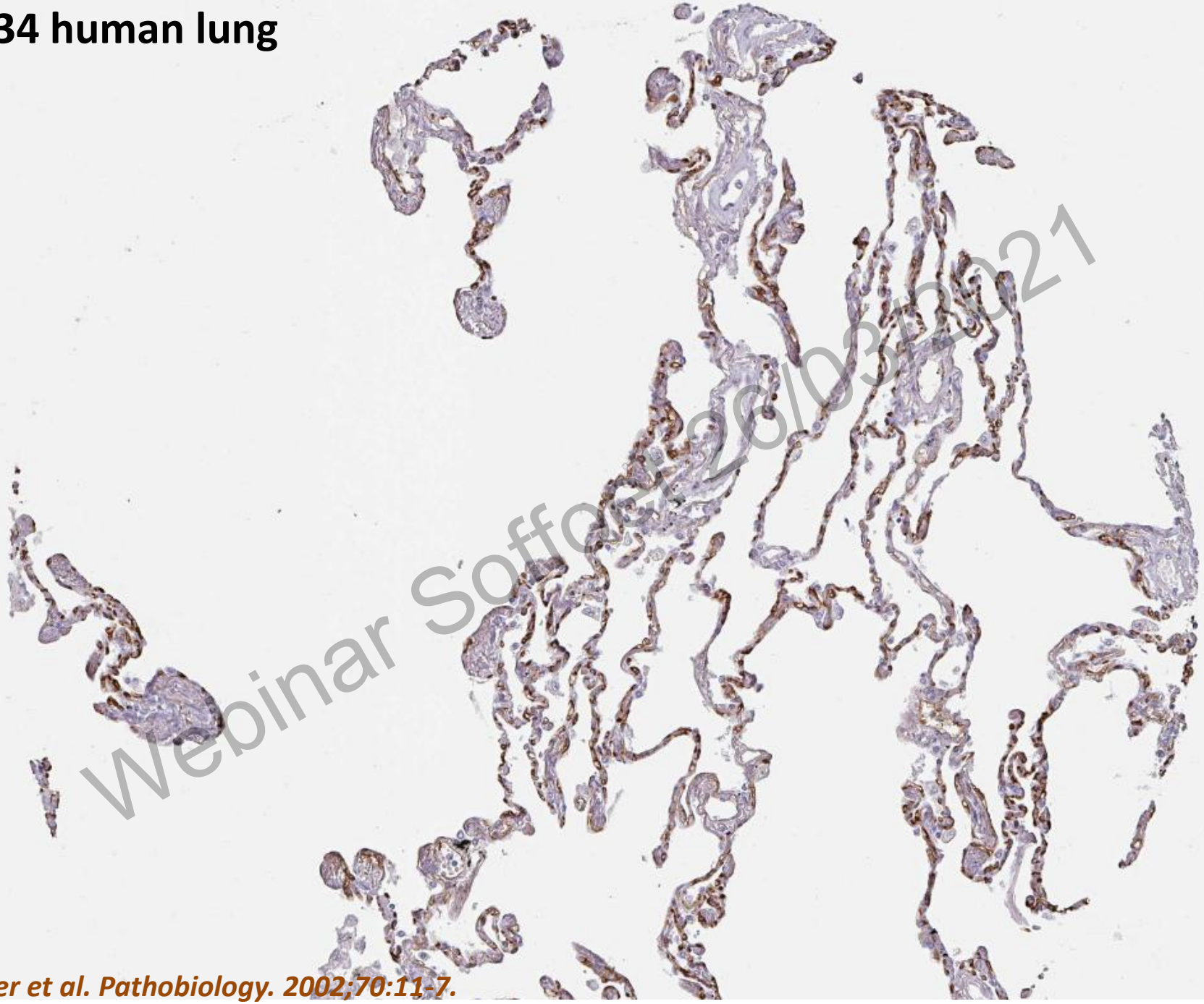
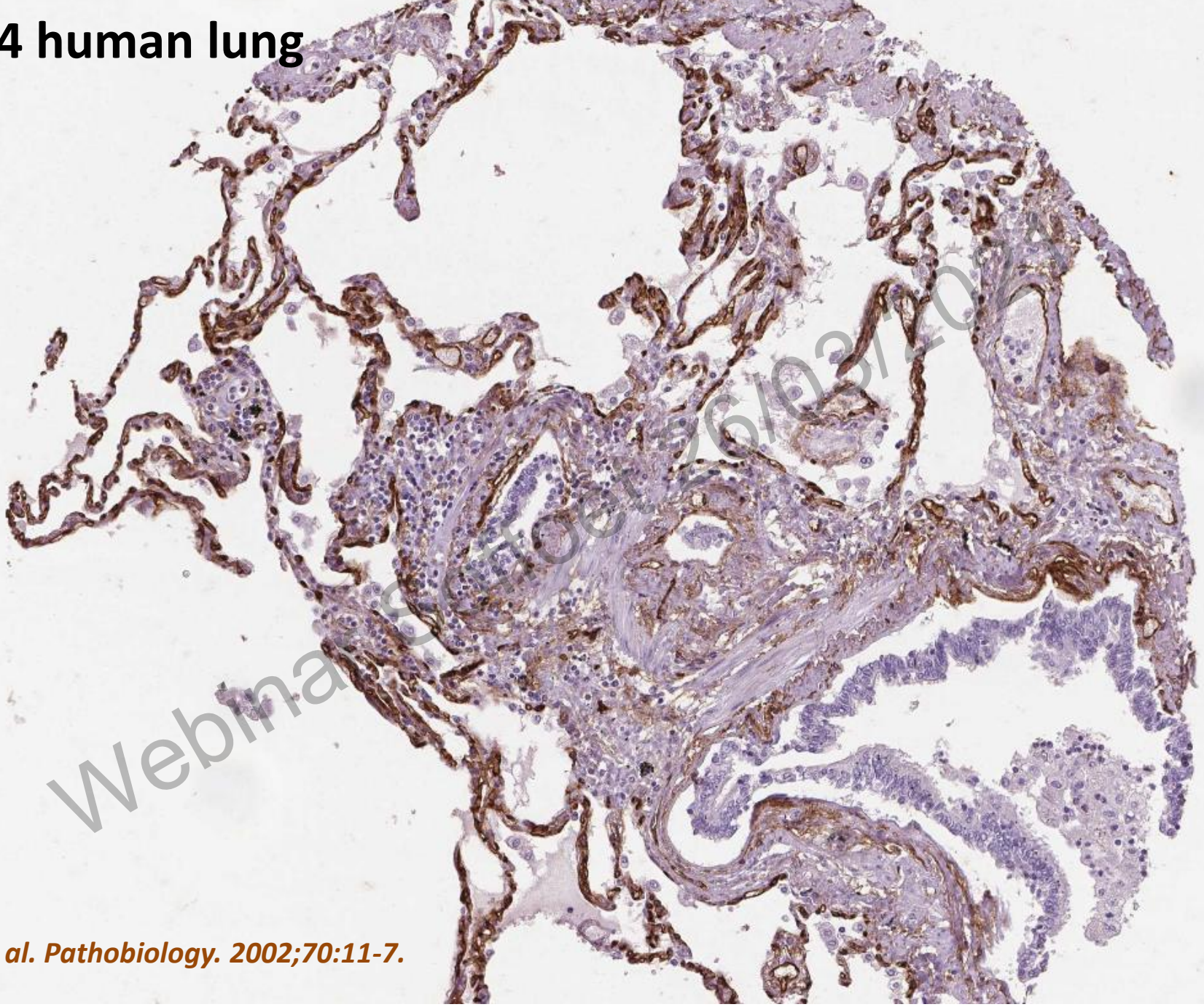
CD34 human lung



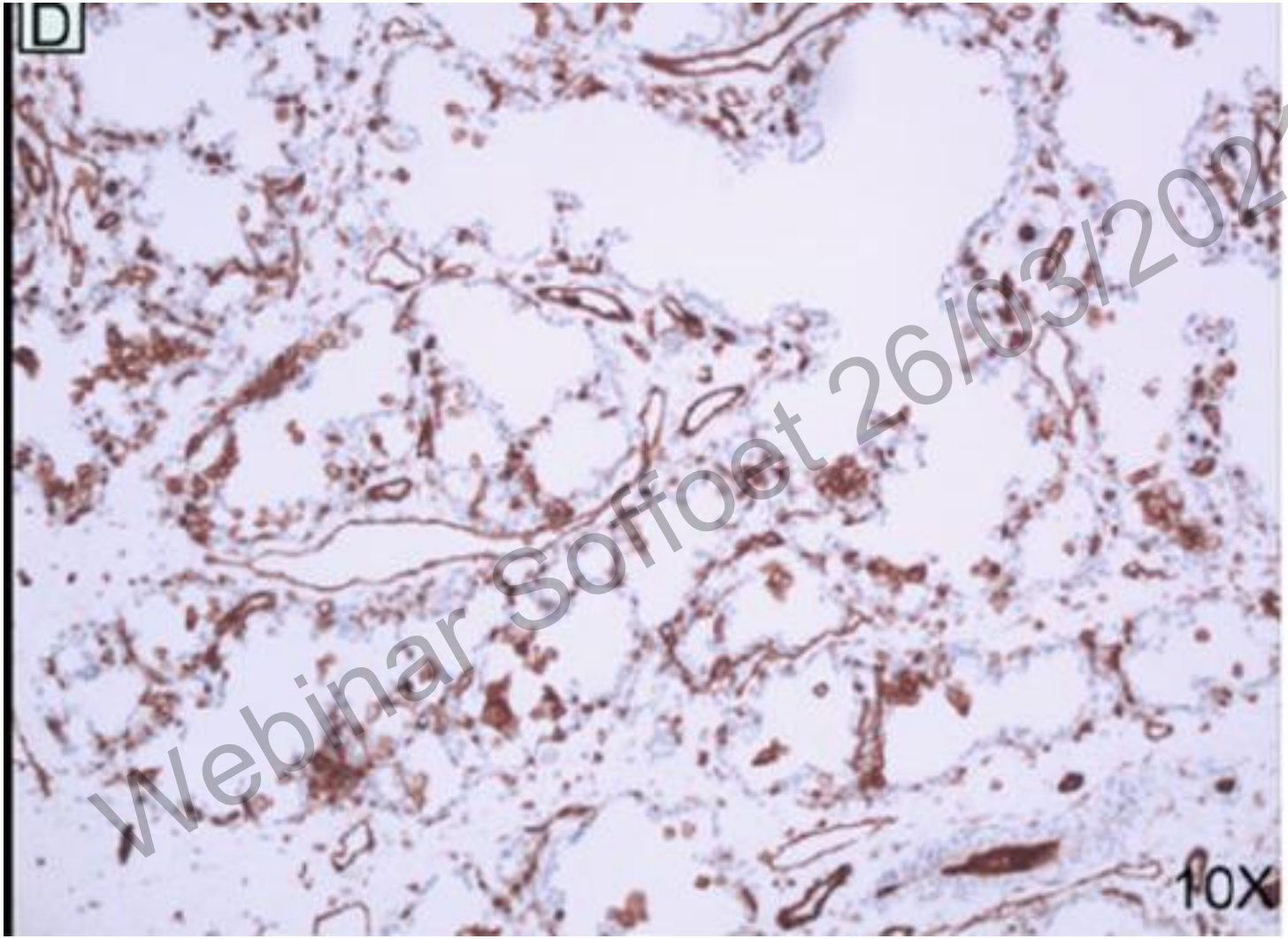
Müller et al. Pathobiology. 2002;70:11-7.

CD34 human lung



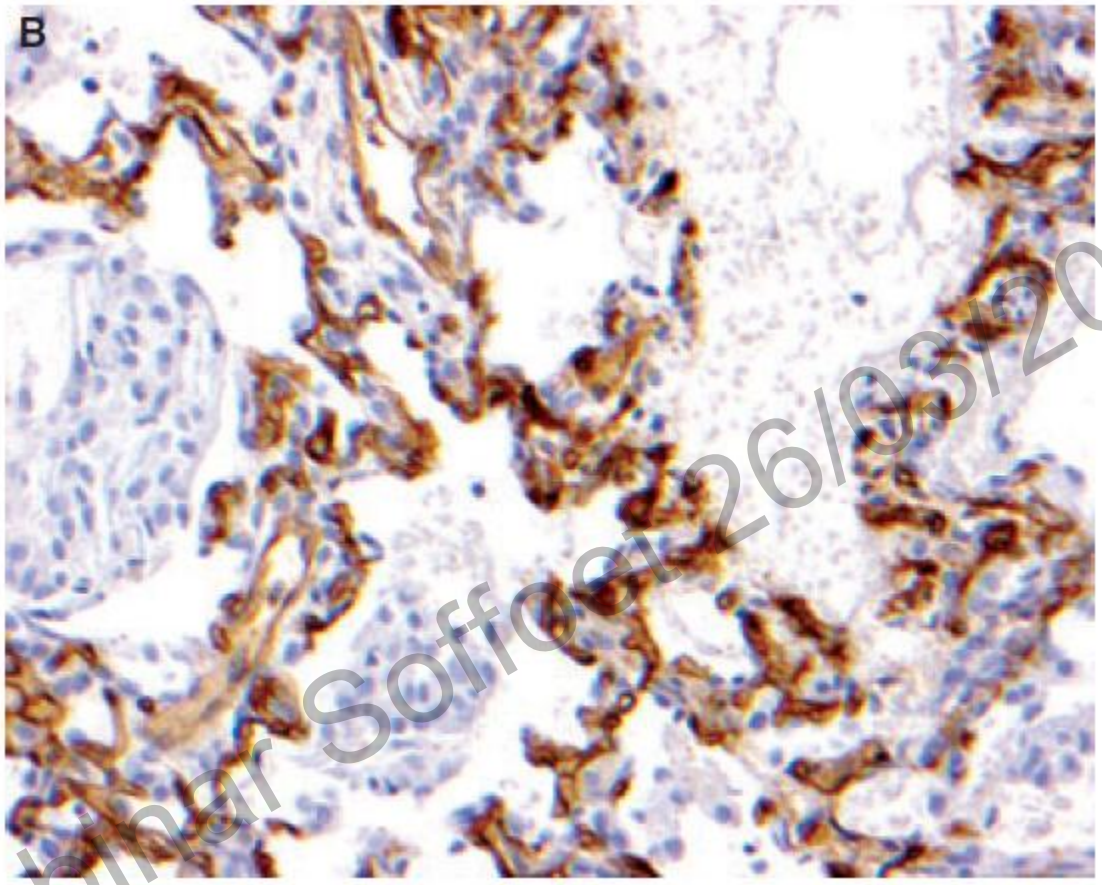
Müller et al. Pathobiology. 2002;70:11-7.

CD34 ACD patient



Edwards et al. J Pediatr. 2019; 210: 214–19

CD34 ACD patient



Melly et al. Histopathology 2008, 53, 450–57

Counting vessels in this context is simply not feasible

Quantitative analysis of capillary morphology in Alveolar Capillary Dysplasia (ACD): a pilot study on two cases and one age-matched control

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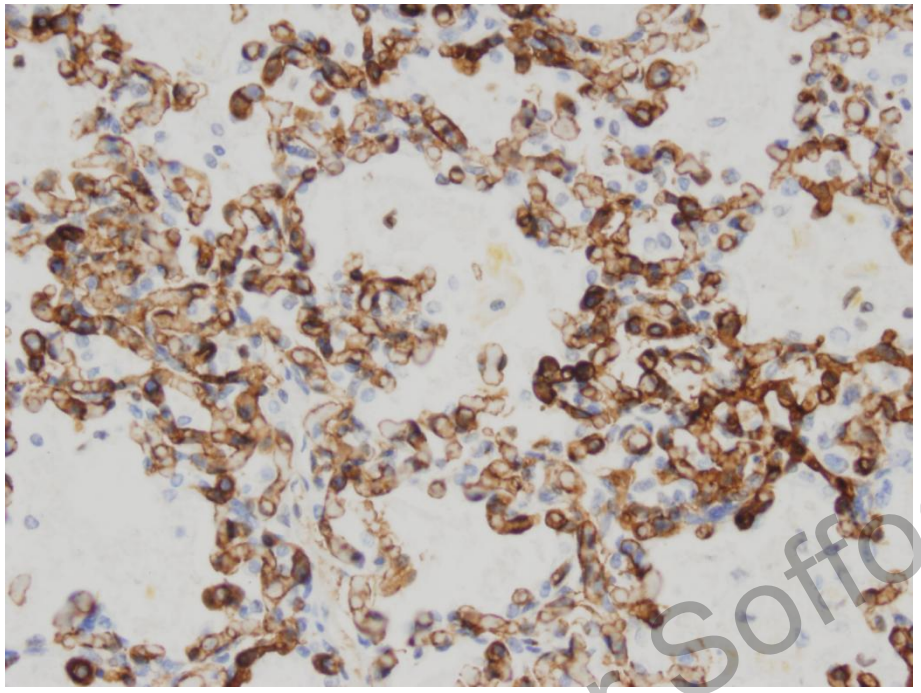
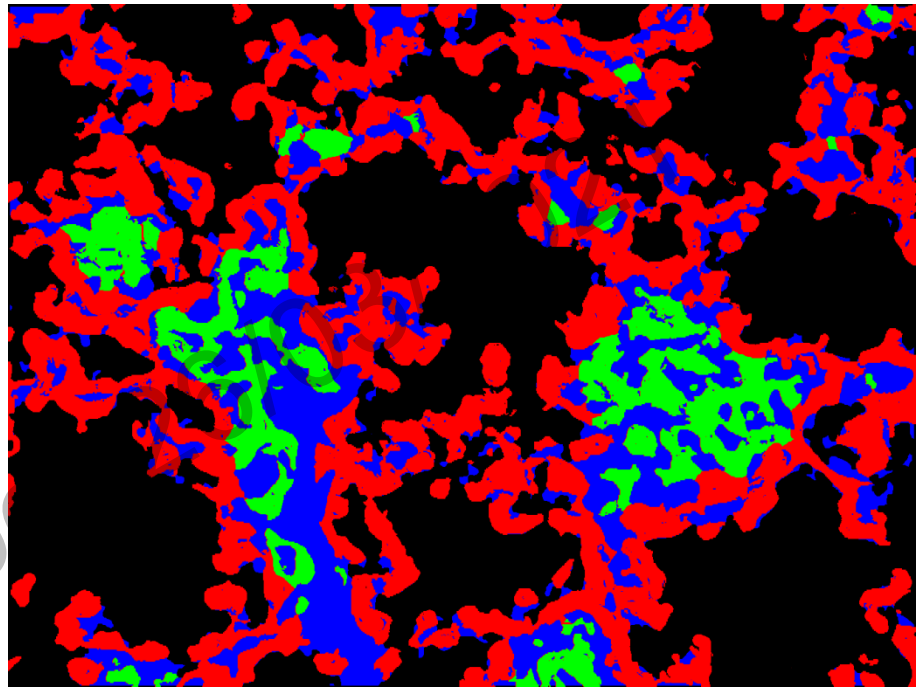
SOFFOET March 2021

CD34 in this report



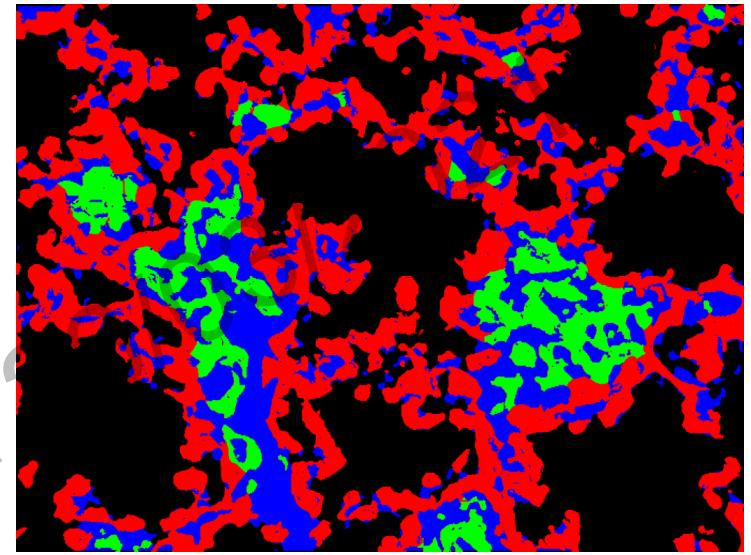


Interstitium/airspaces = 0.91

Vessels/interstitium (%) = 94

Vessels not in contact (%) = 19

Measured parameters



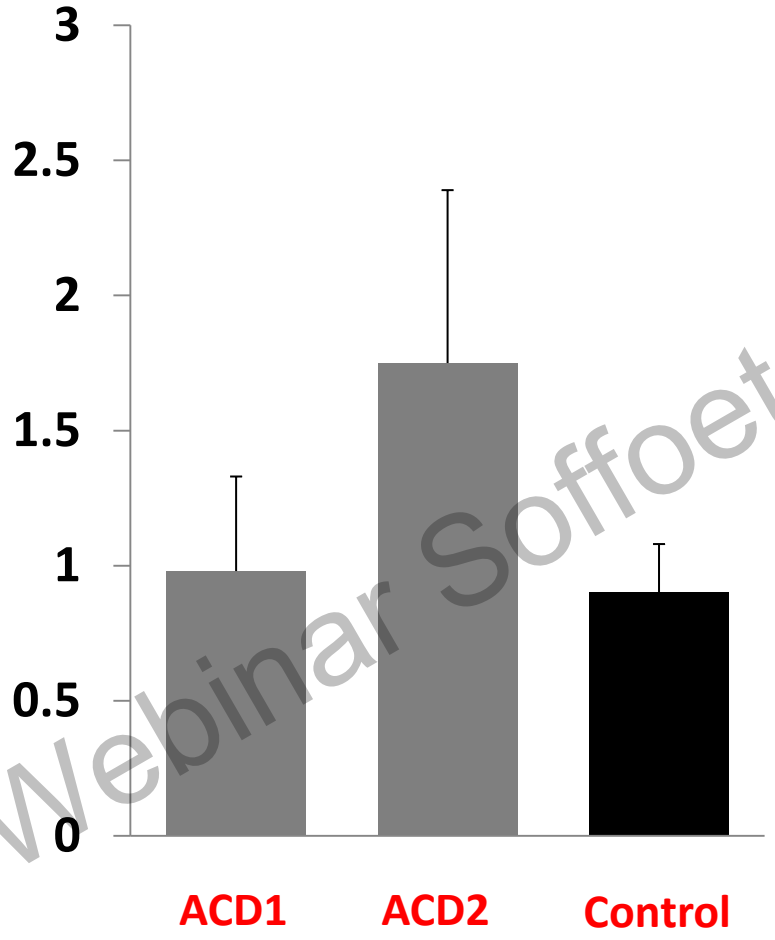
- interstitium / airspaces ratio:
  all that is not black / black

- vessel area / interstitial area %:
  red + green / red + green + blue (%)

- vessel area not in contact with airspaces / all vessel area %:
  green / red + green (%)

Mann & Whitney U test, units of measurement are microscopic fields x 20
(control n = 7, ACD1 n = 10, ACD2 n = 8)

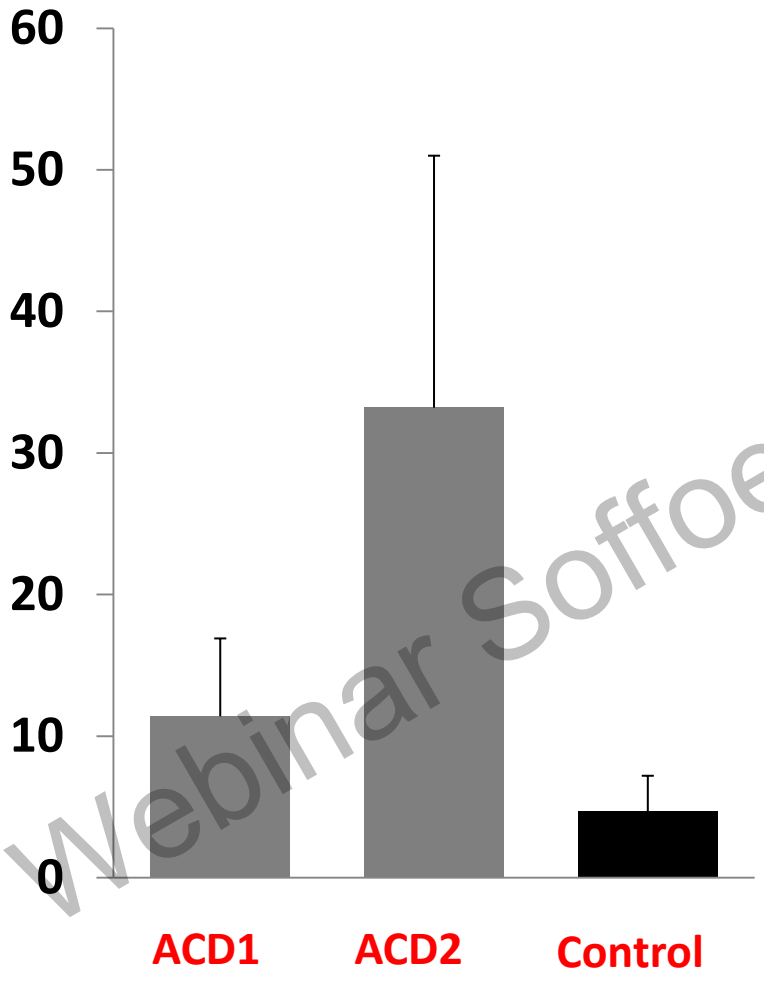
Results 1: interstitium / airspaces ratio



ACD1 *vs*. Control NS

ACD2 *vs*. Control p < 0.009

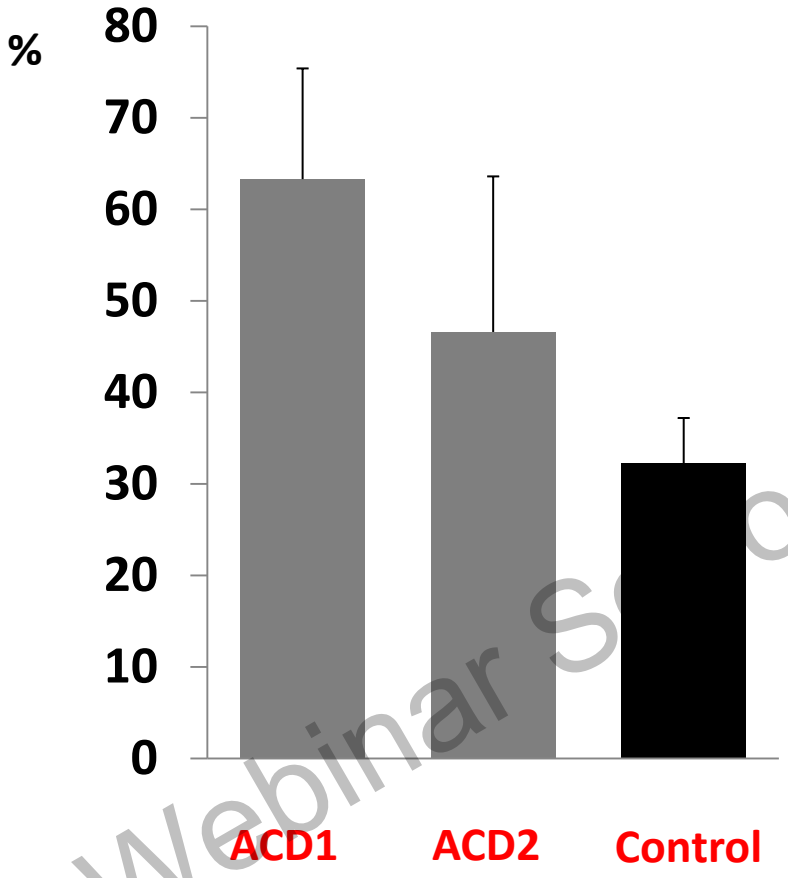
Results 2: vessel area not in contact with airspaces / all vessel area %



ACD1 *vs.* Control $p < 0.01$

ACD2 *vs.* Control $p < 0.0001$

Results 3: vessel area / interstitial area %

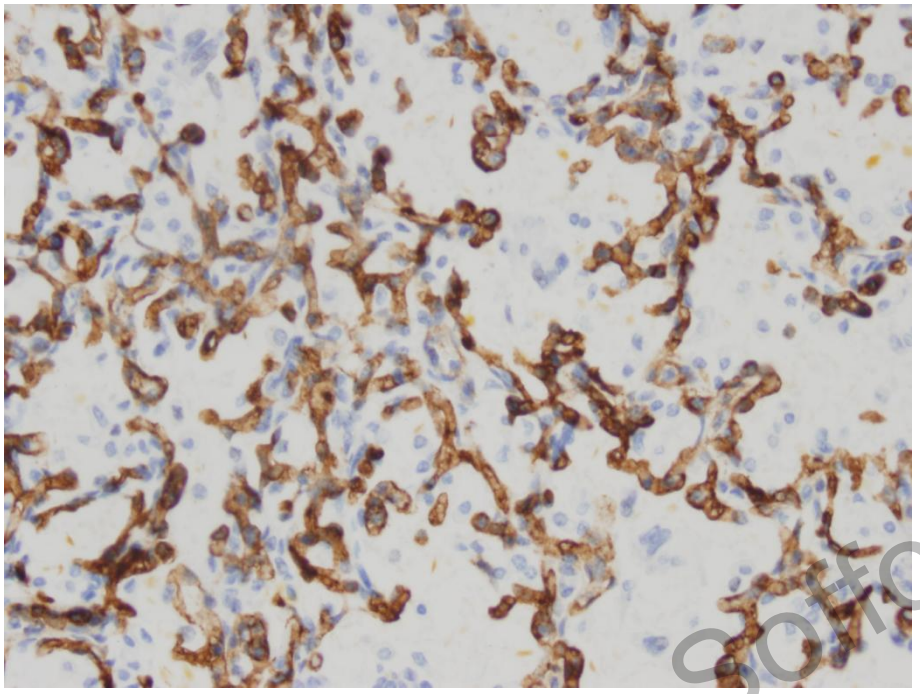


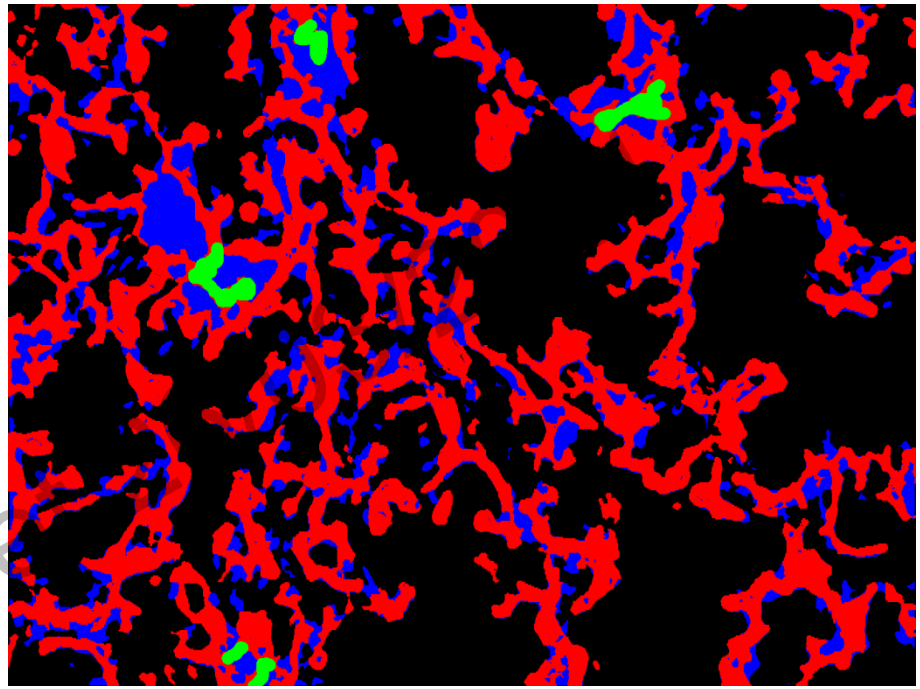
ACD1 *vs*. Control p < 0.008

ACD2 *vs*. Control p < 0.005

ACD1

#1



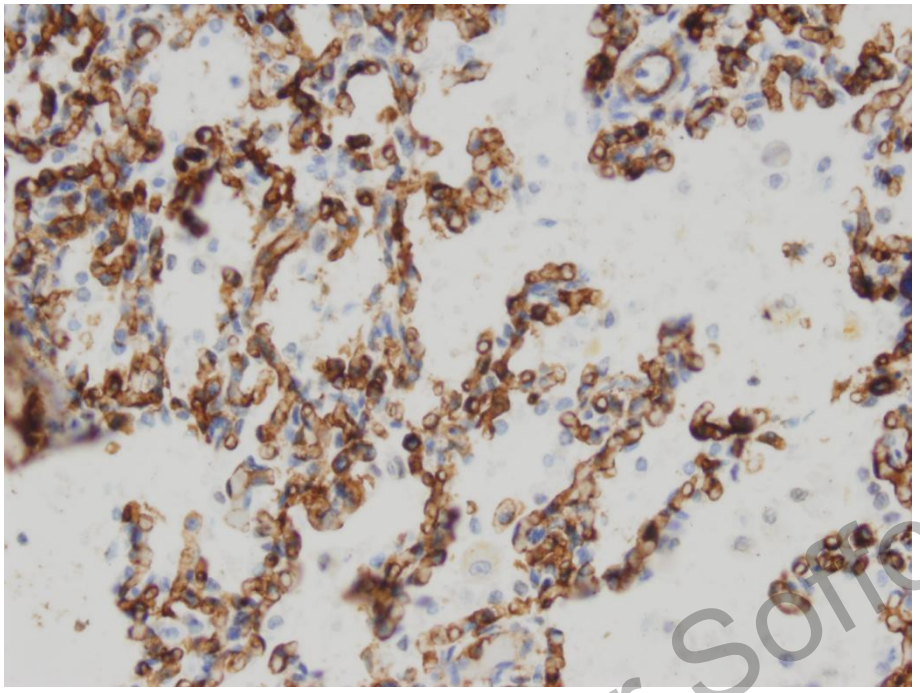


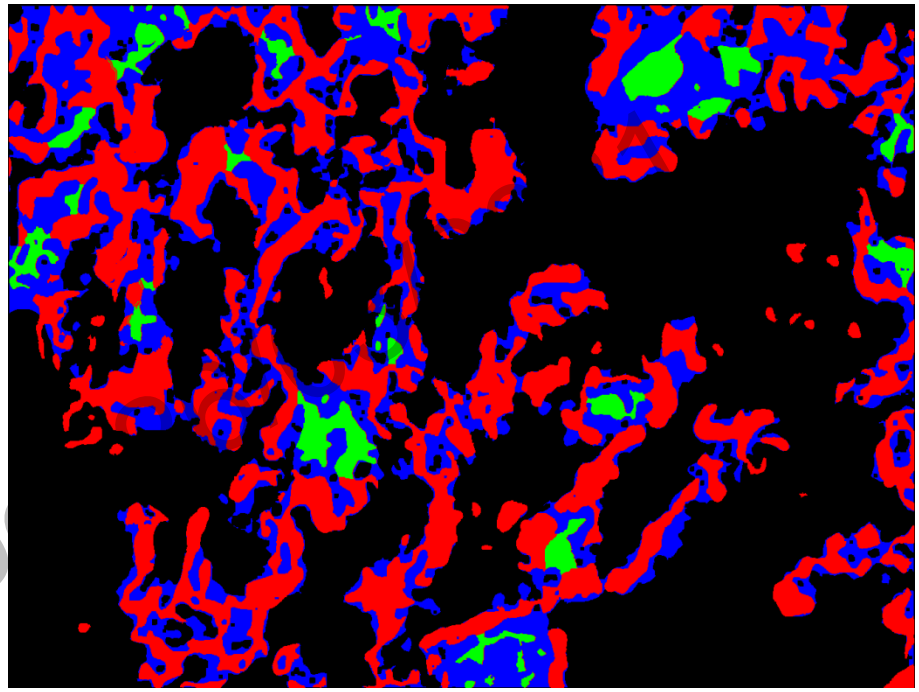
Interstitium/airspaces = 0.78

Vessels/interstitium (%) = 68

Vessels not in contact (%) = 3

#2



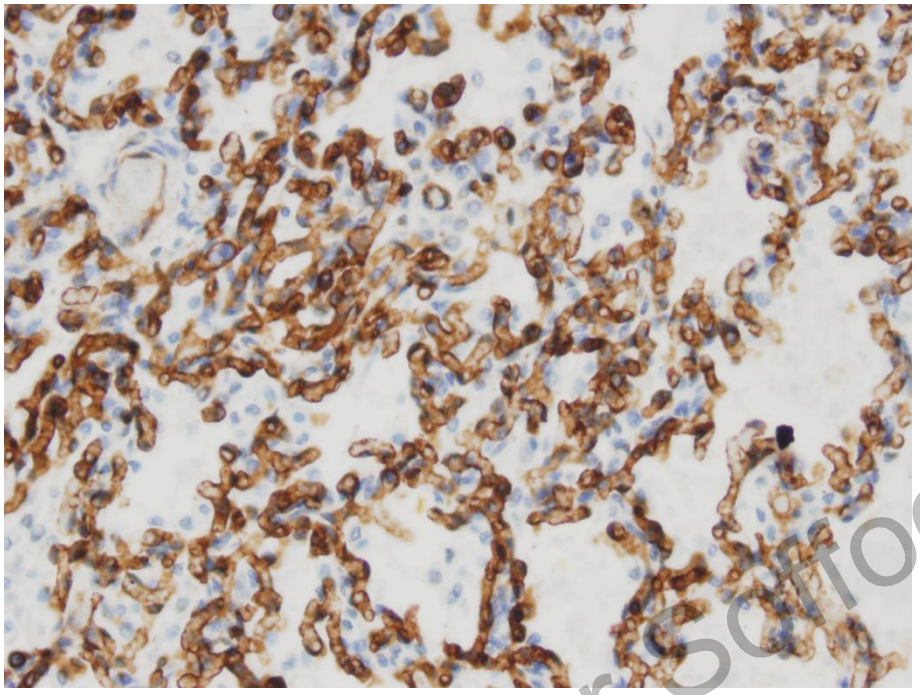


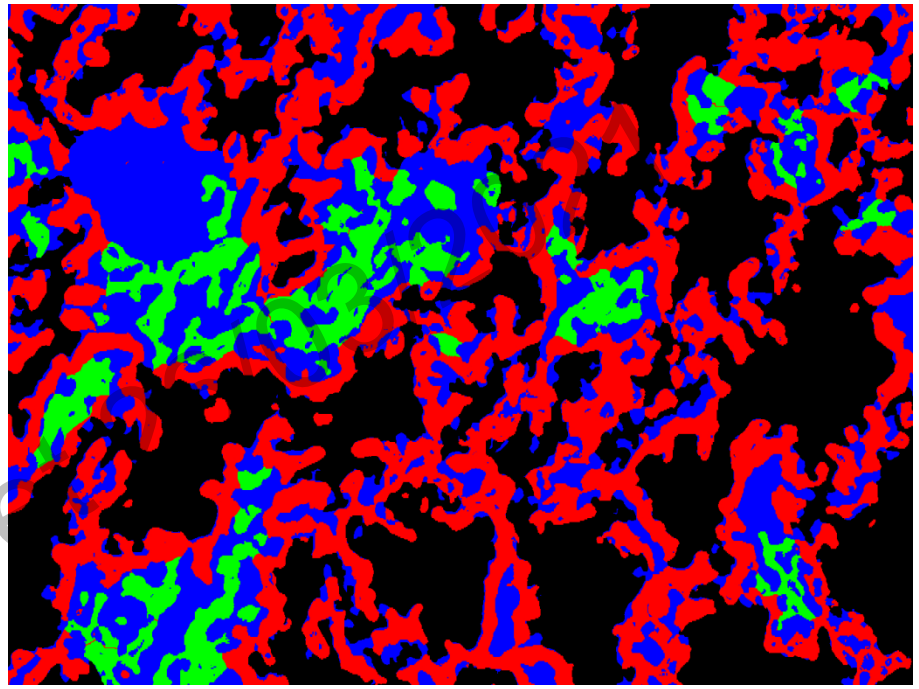
Interstitium/airspaces = 0.91

Vessels/interstitium (%) = 54

Vessels not in contact (%) = 17

#3



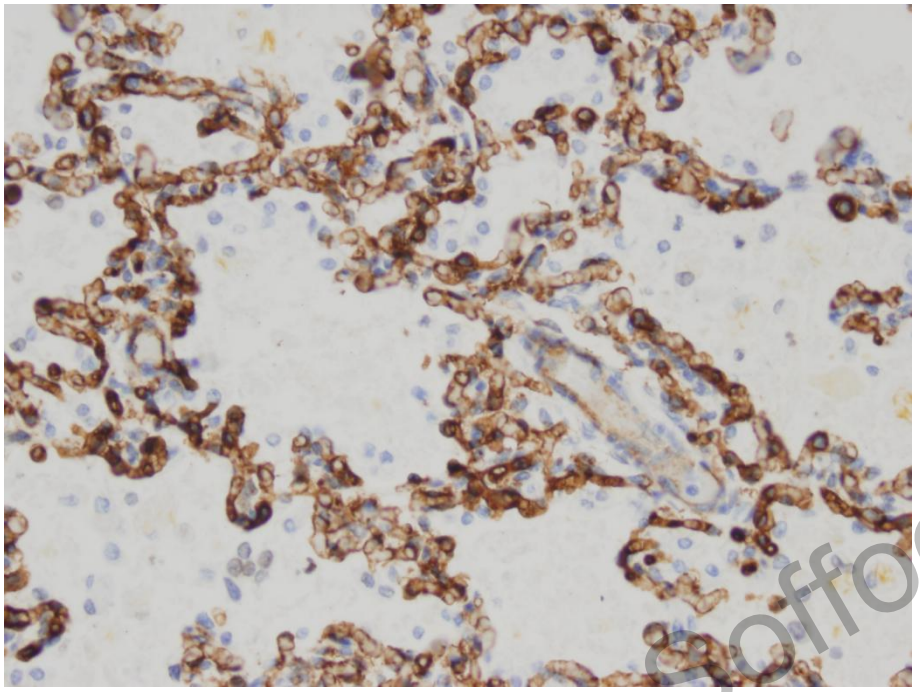


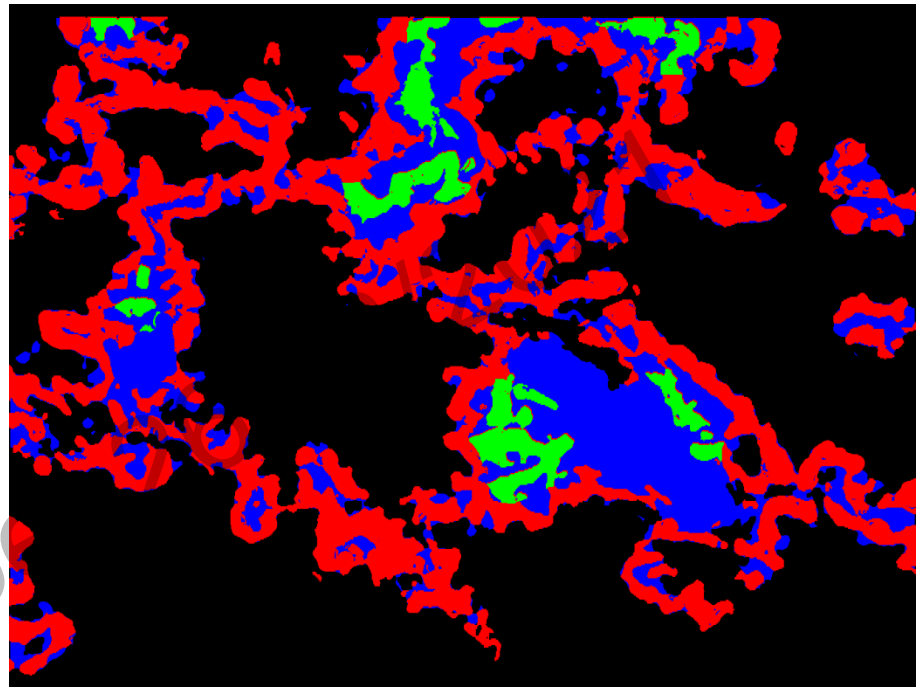
Interstitium/airspaces = 1.82

Vessels/interstitium (%) = 60

Vessels not in contact (%) = 19.0

#4



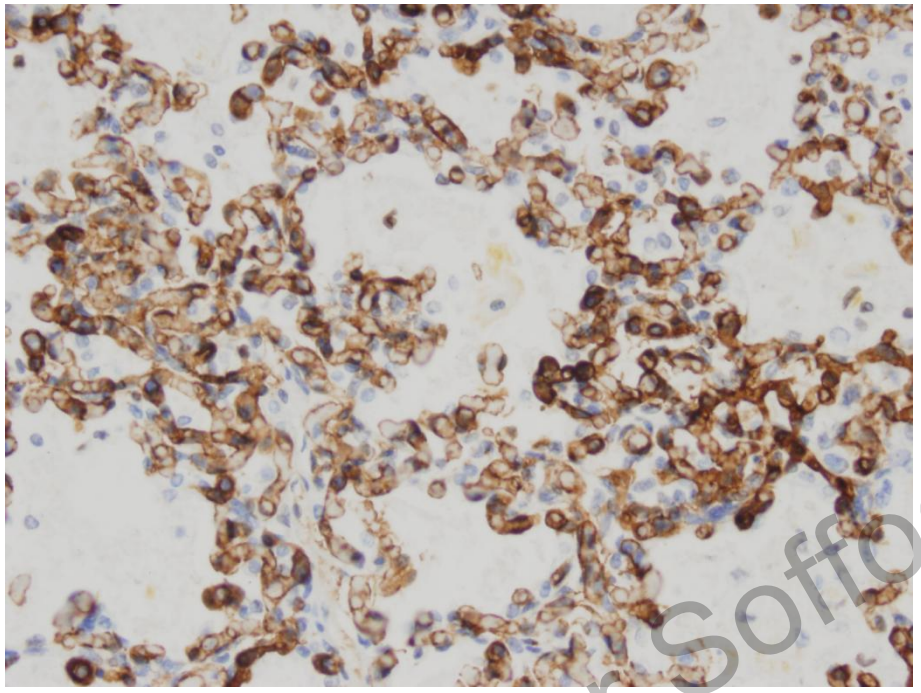


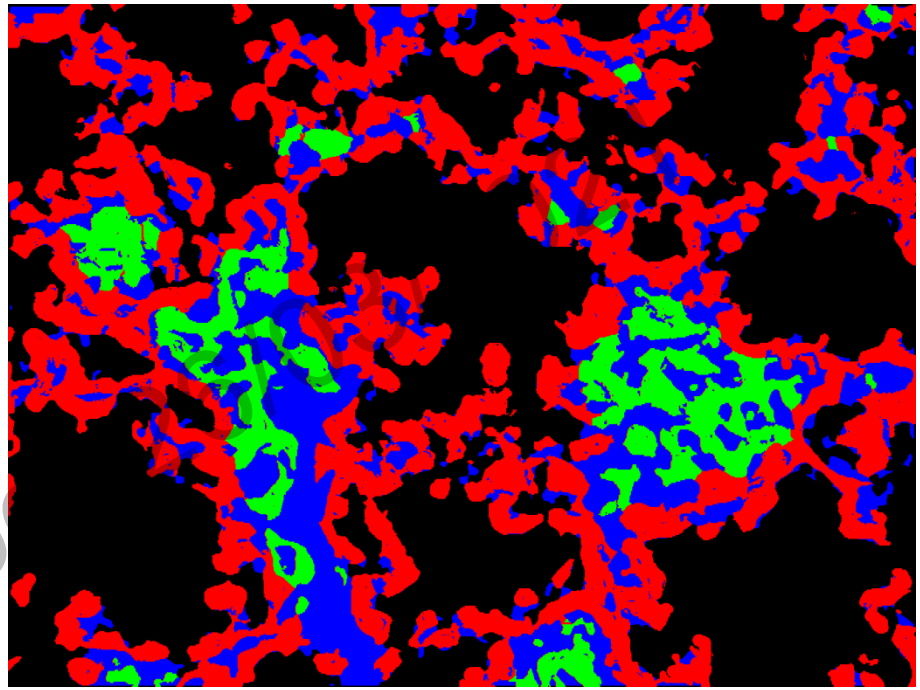
Interstitium/airspaces = 0.91

Vessels/interstitium (%) = 54

Vessels not in contact (%) = 9

#5



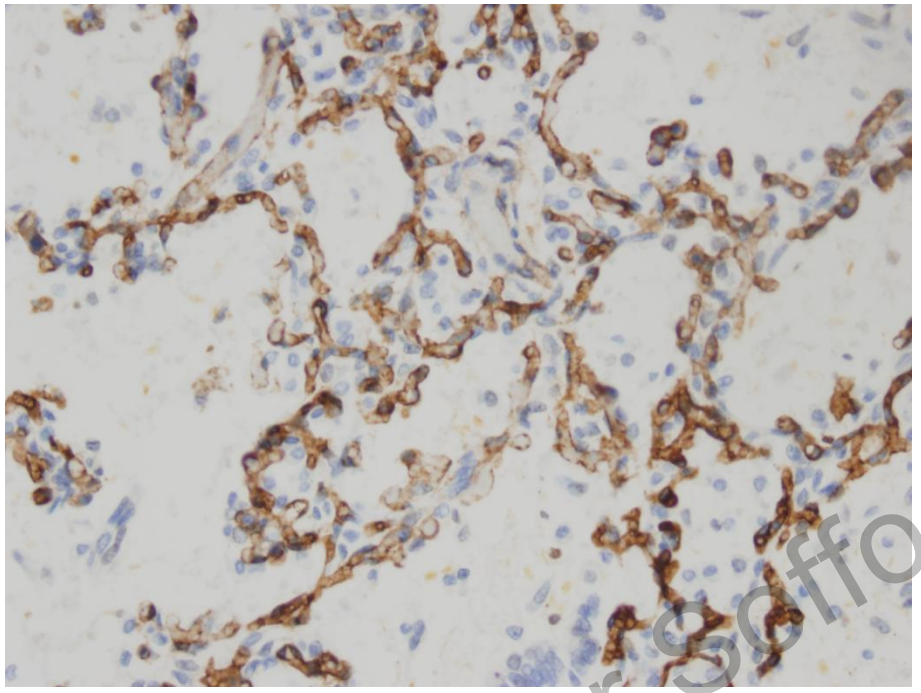


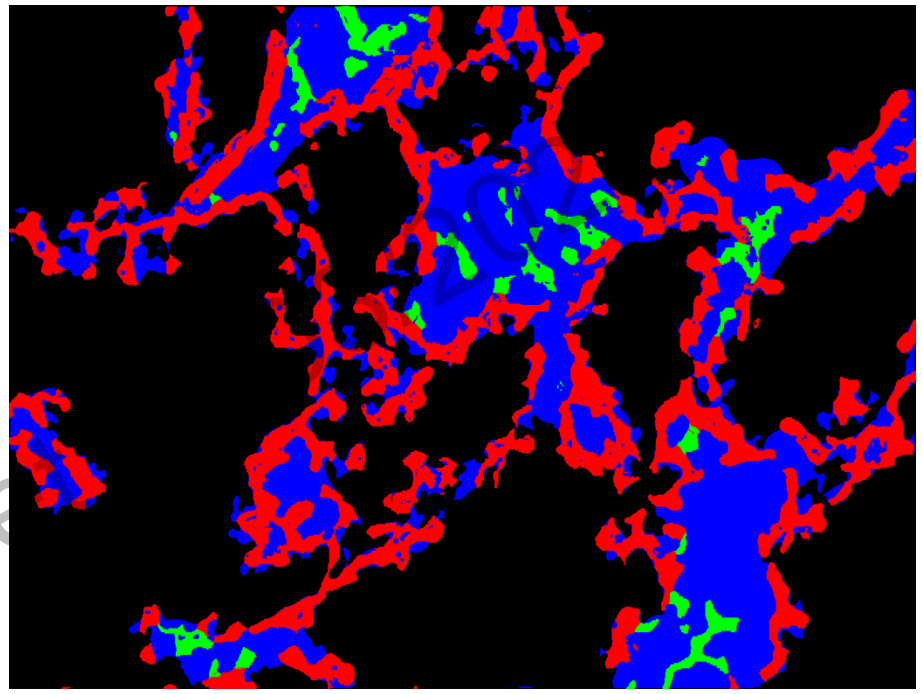
Interstitium/airspaces = 0.91

Vessels/interstitium (%) = 94

Vessels not in contact (%) = 19

#7



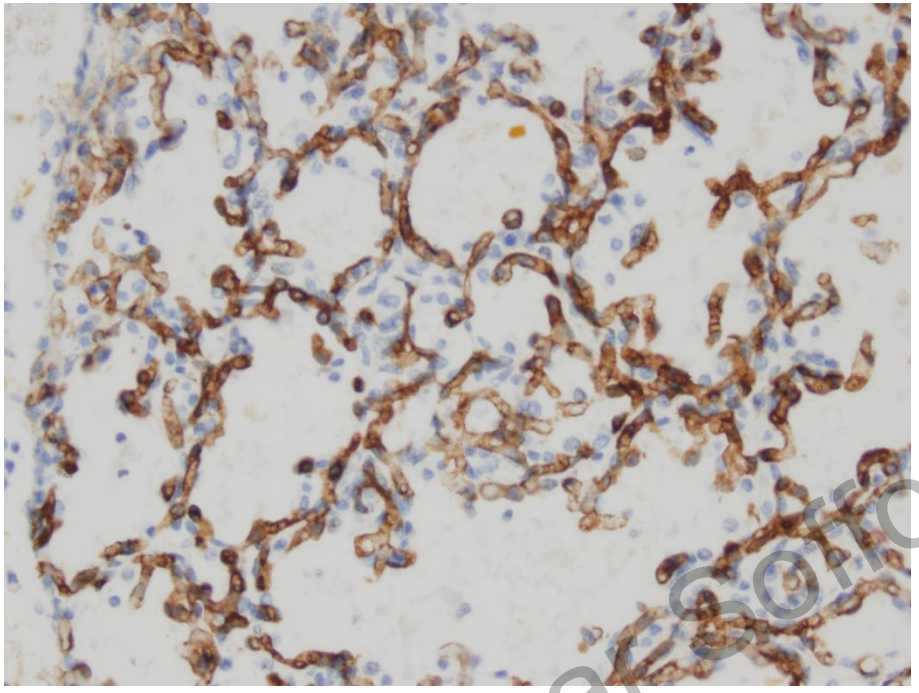


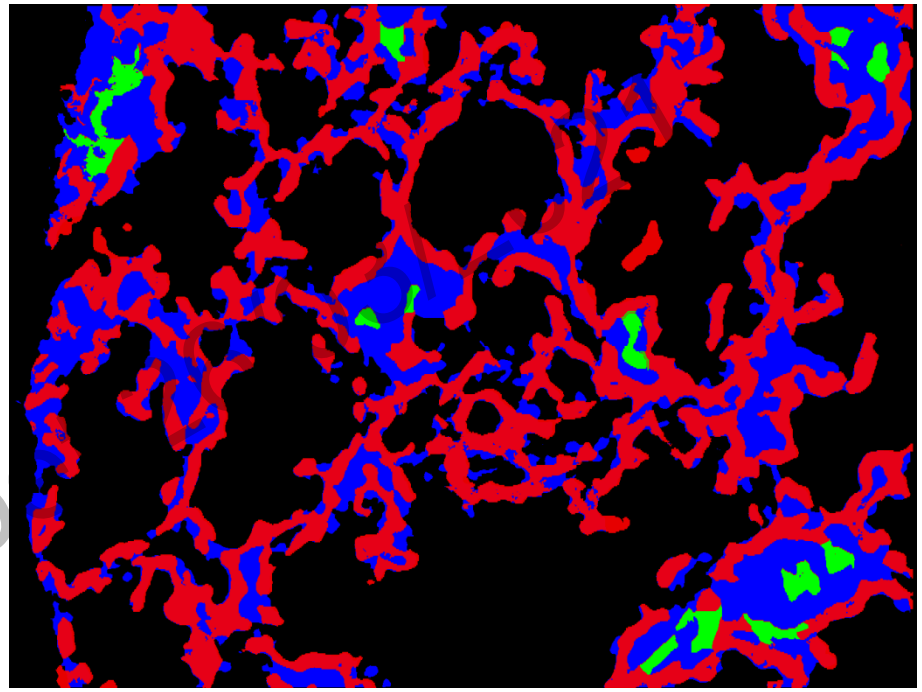
Interstitium/airspaces = 0.67

Vessels/interstitium (%) = 52

Vessels not in contact (%) = 10

#8



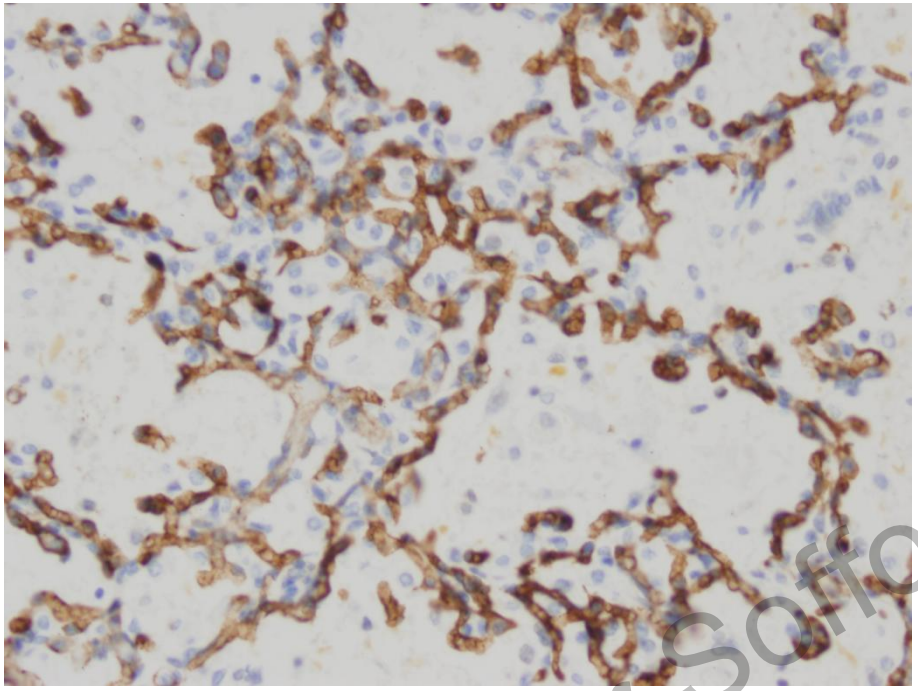


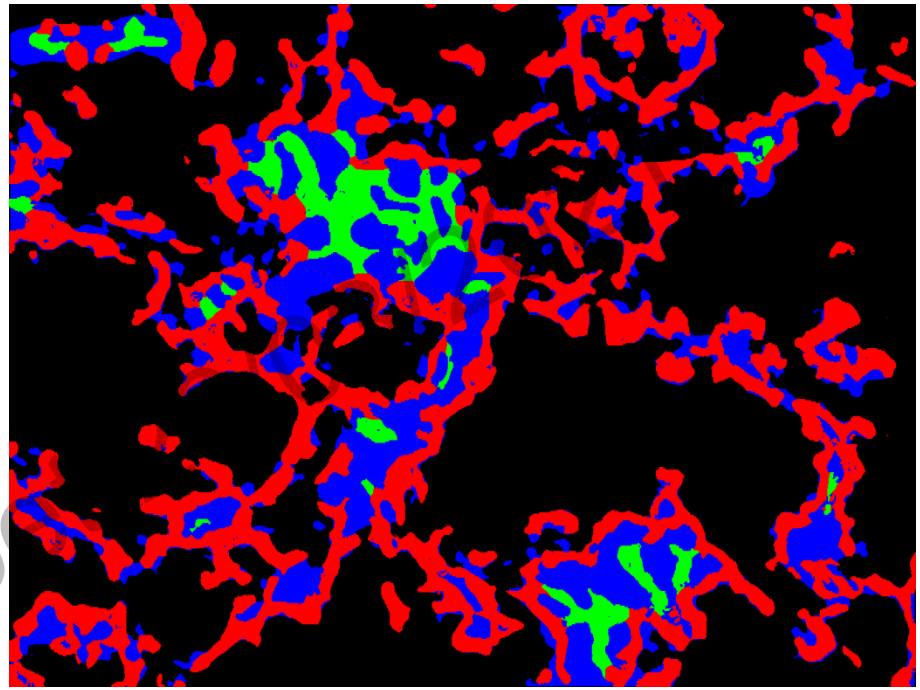
Interstitium/airspaces = 0.84

Vessels/interstitium (%) = 59

Vessels not in contact (%) = 5

#9



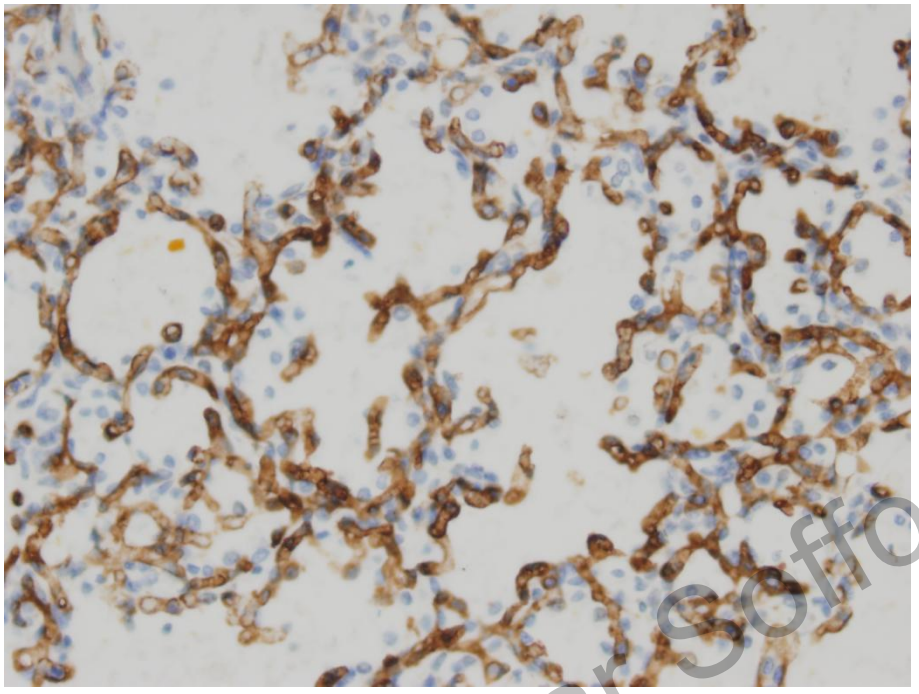


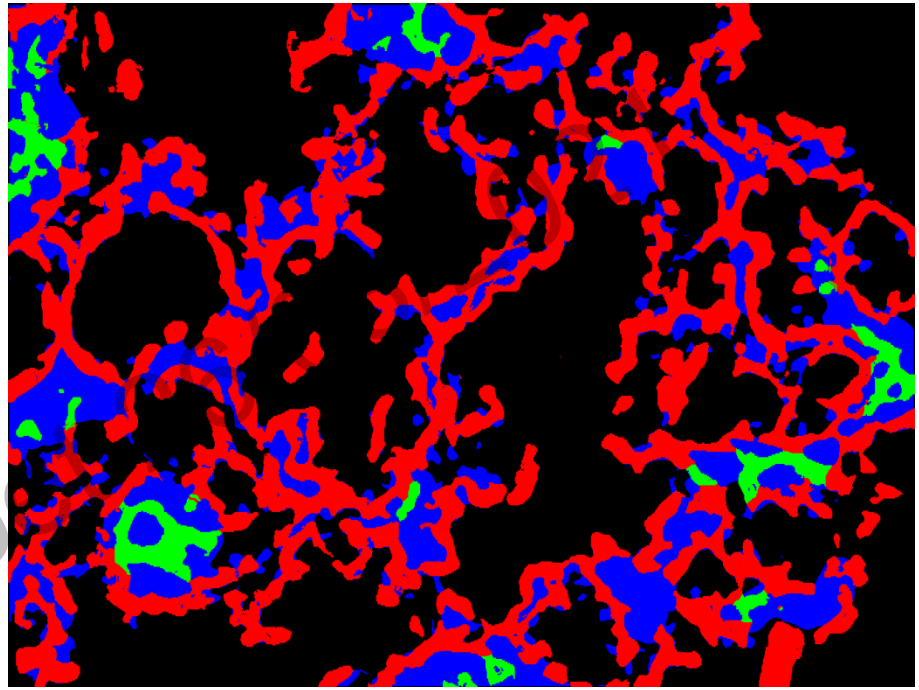
Interstitium/airspaces = 0.75

Vessels/interstitium (%) = 61

Vessels not in contact (%) = 12

#11



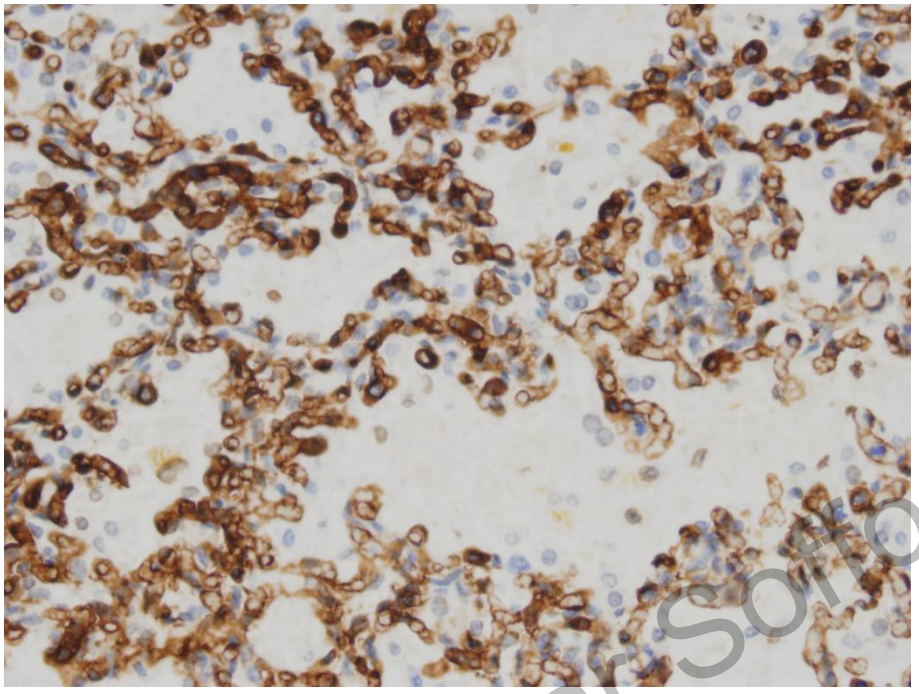


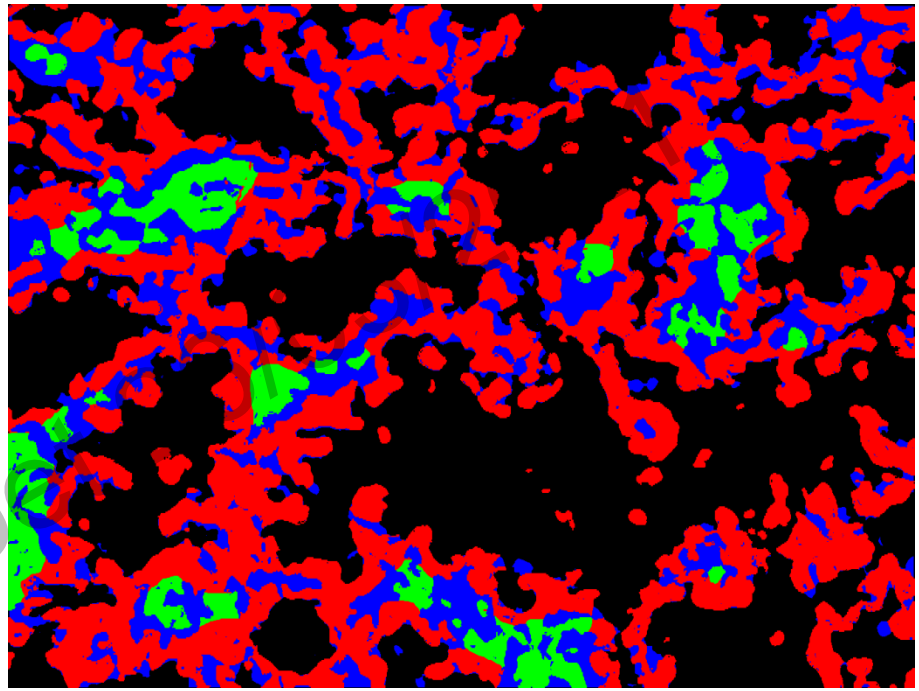
Interstitium/airspaces = 0.86

Vessels/interstitium (%) = 64

Vessels not in contact (%) = 8

#12





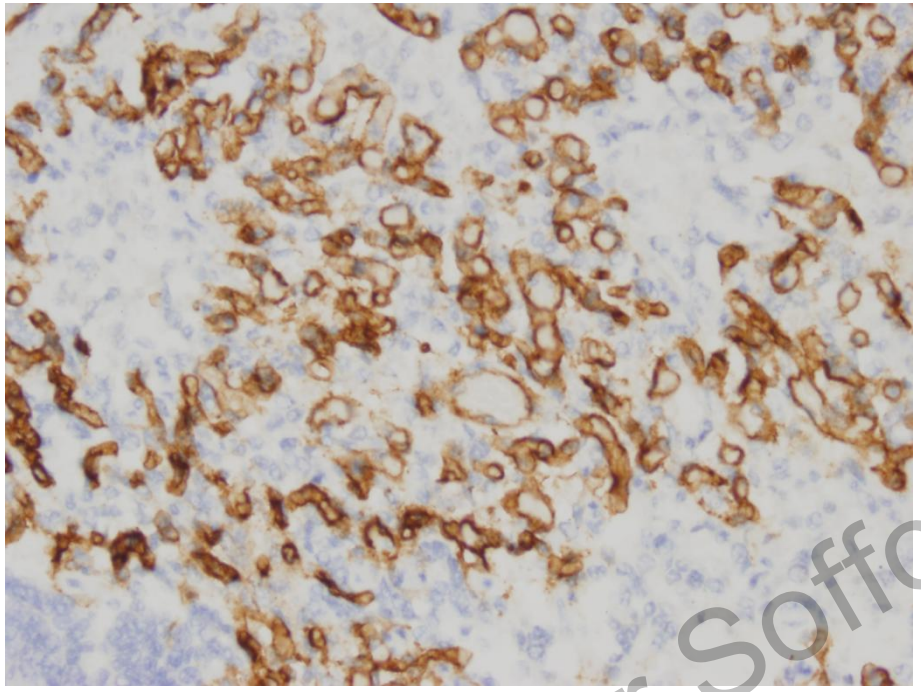
Interstitium/airspaces = 1.37

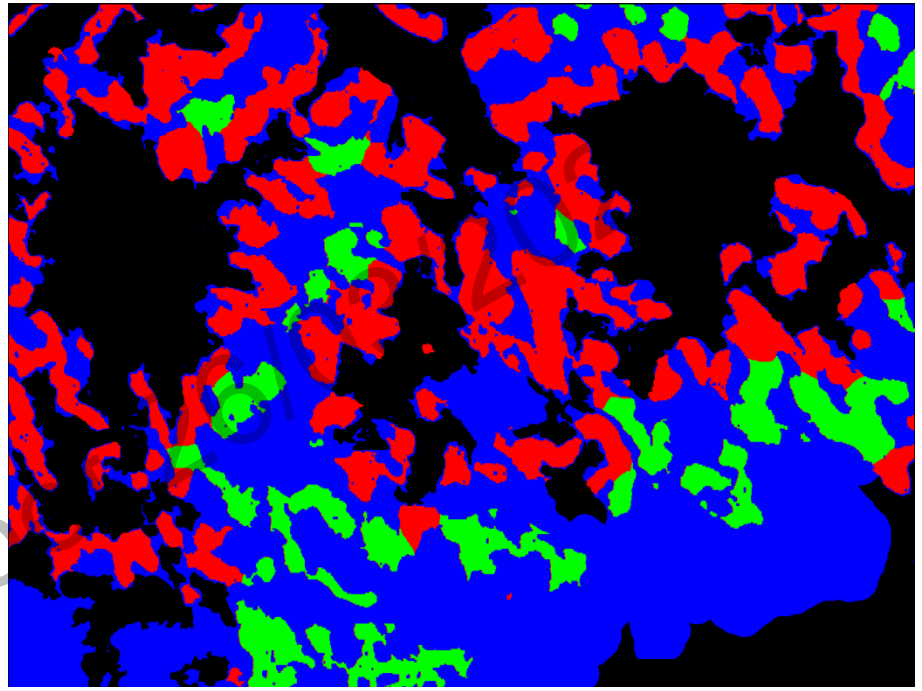
Vessels/interstitium (%) = 69

Vessels not in contact (%) = 13

ACD2

#1



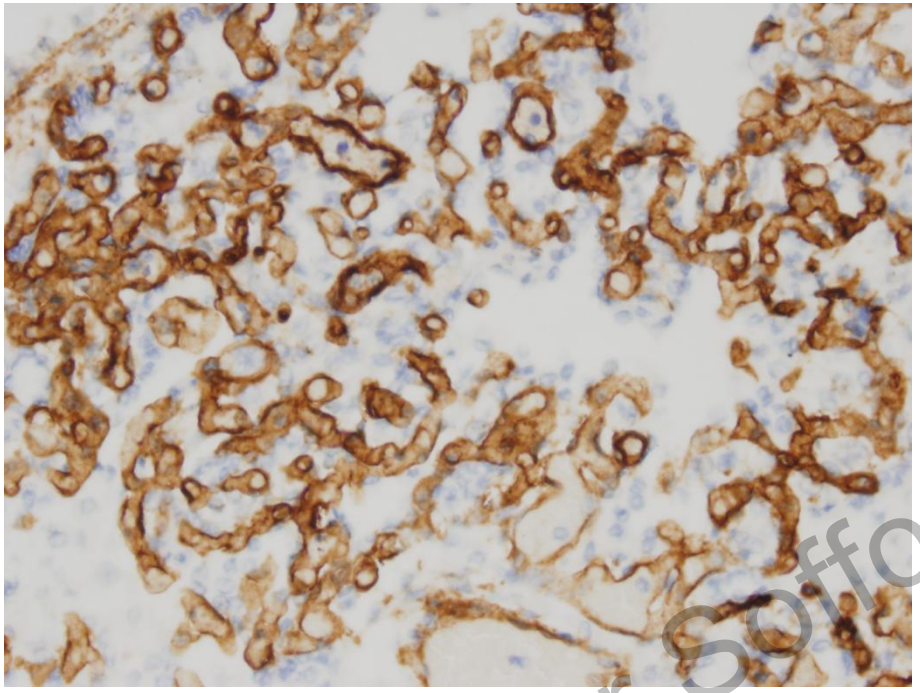


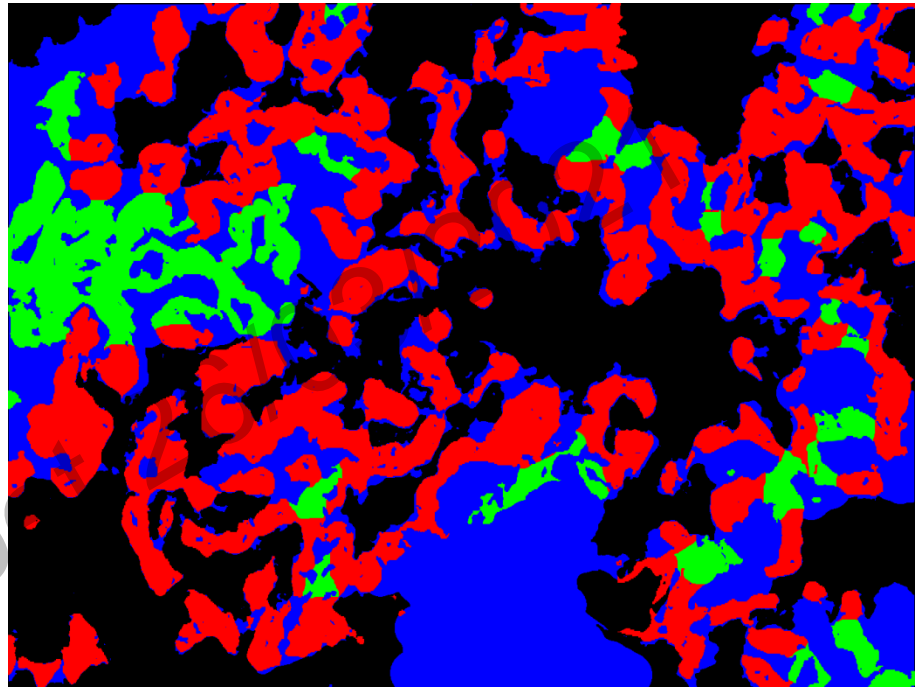
Interstitium/airspaces = 2.1

Vessels/interstitium (%) = 41

Vessels not in contact (%) = 27

#2



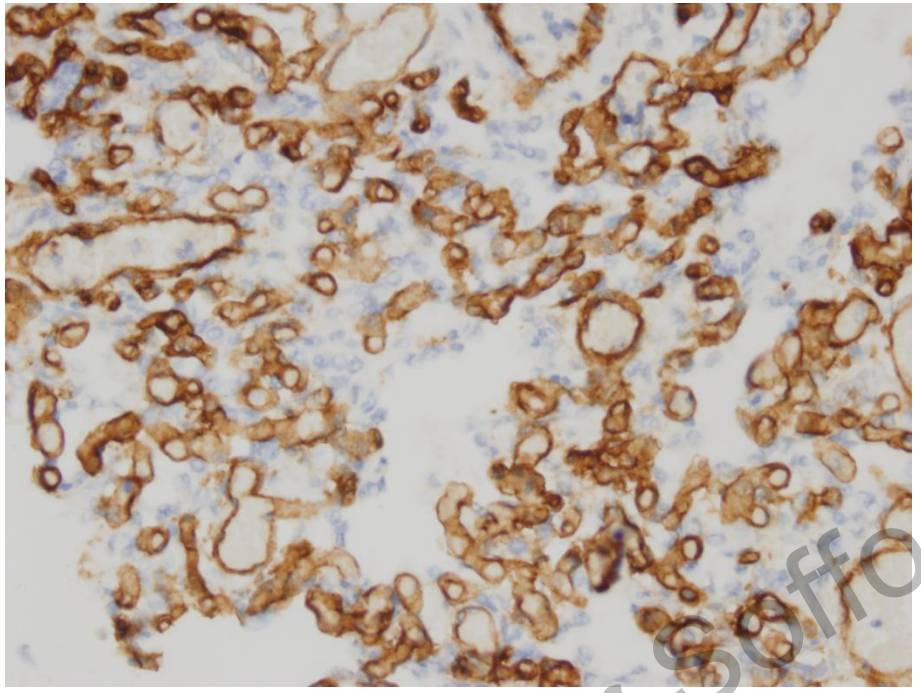


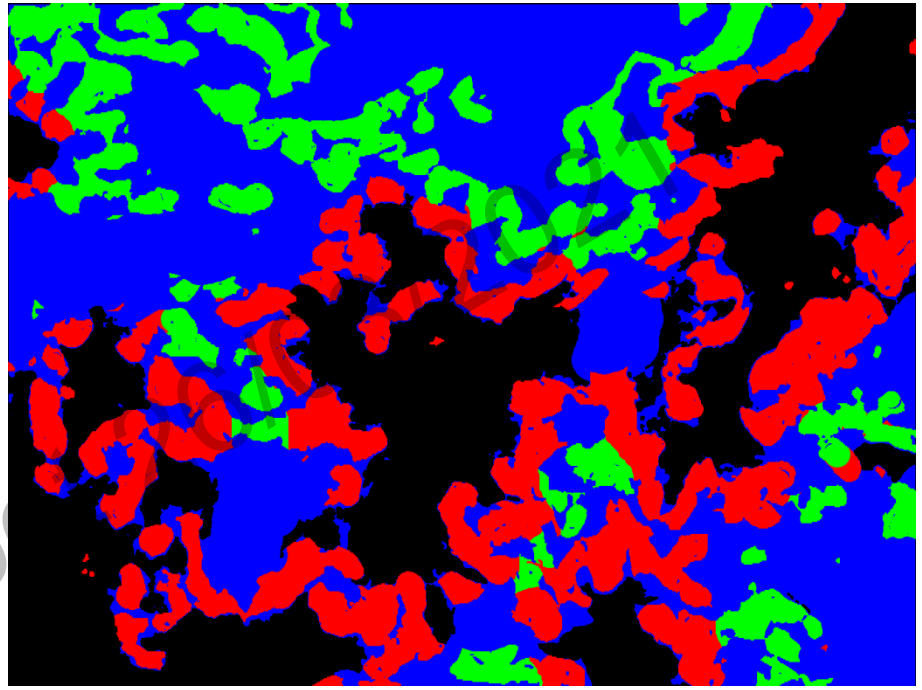
Interstitium/airspaces = 2.1

Vessels/interstitium (%) = 55

Vessels not in contact (%) = 21

#4



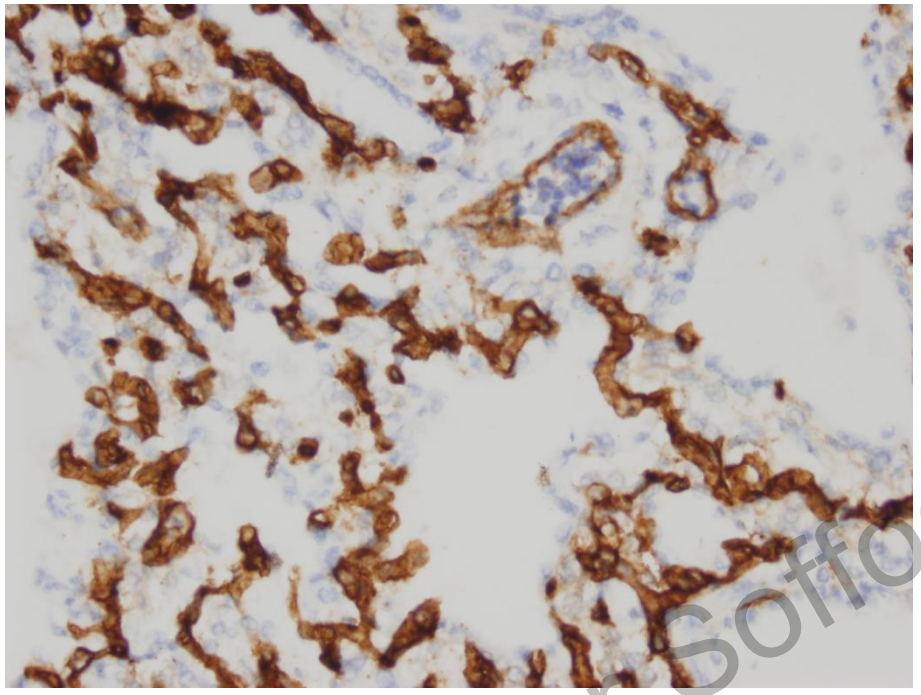


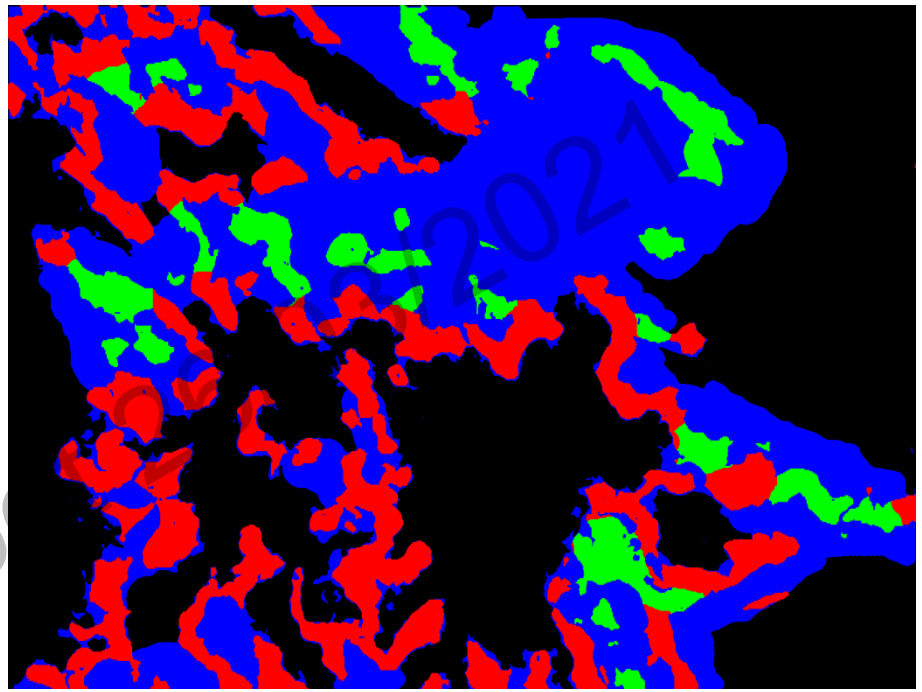
Interstitium/airspaces = 2.9

Vessels/interstitium (%) = 45

Vessels not in contact (%) = 34

#6



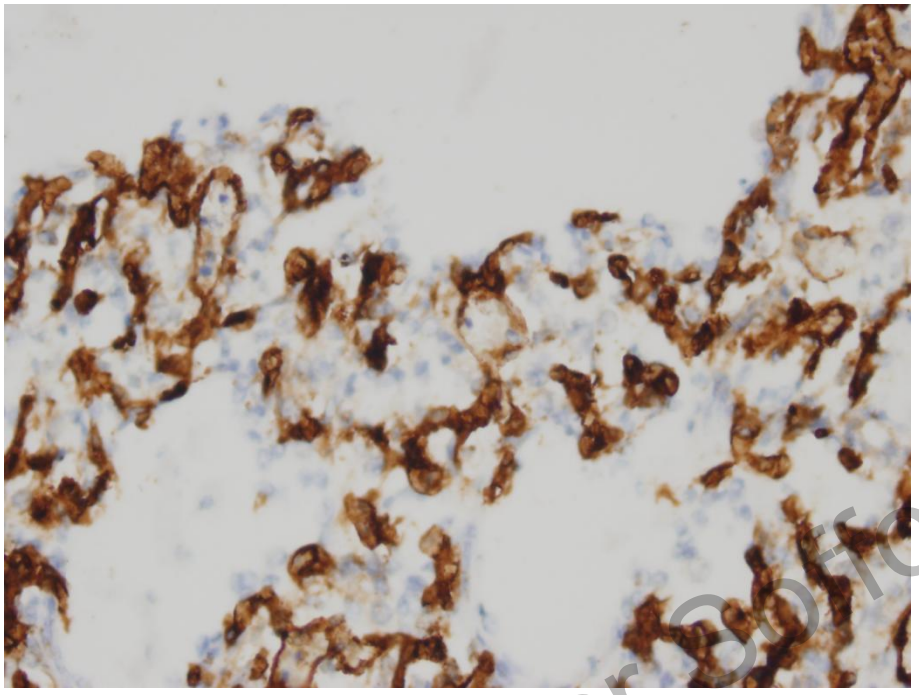


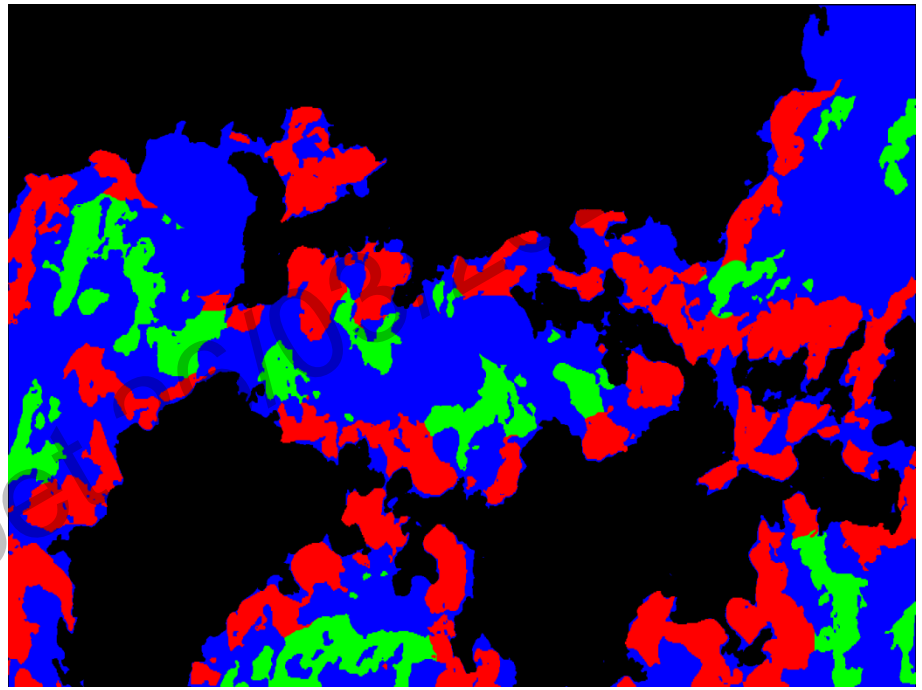
Interstitium/airspaces = 1.3

Vessels/interstitium (%) = 40

Vessels not in contact (%) = 24

#7



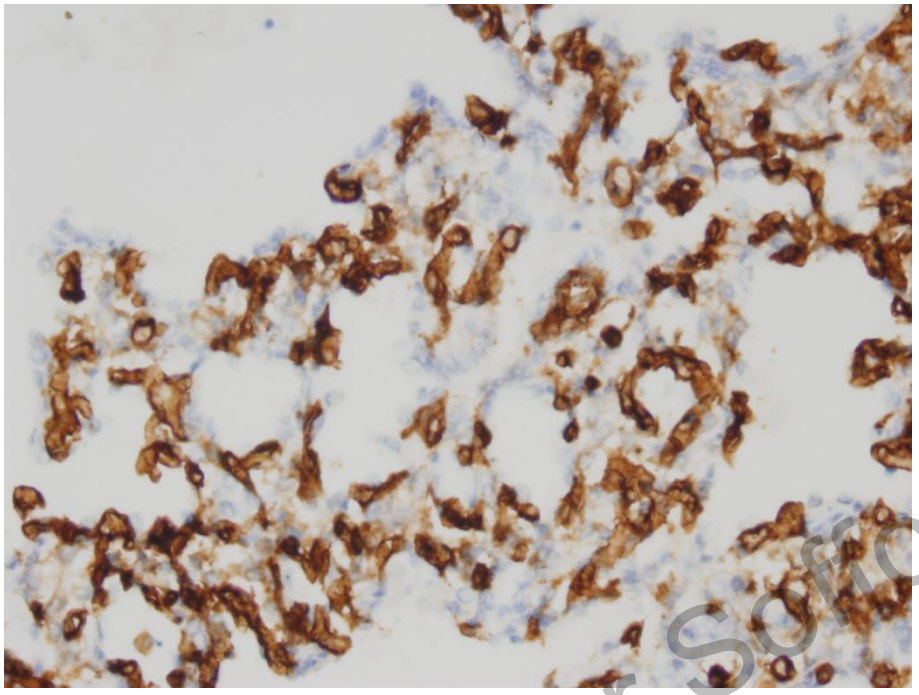


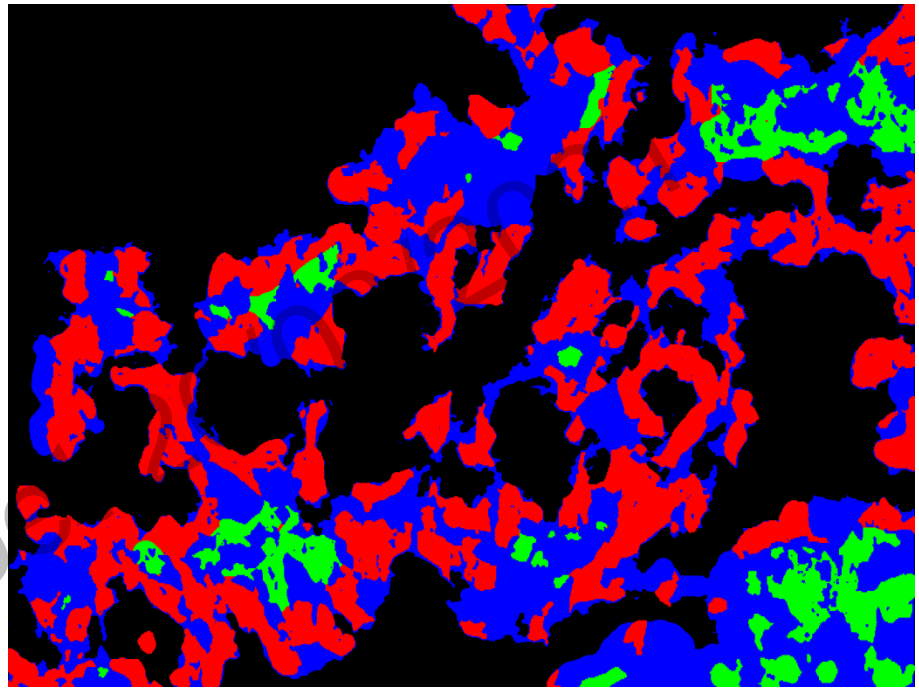
Interstitium/airspaces = 1.1

Vessels/interstitium (%) = 44

Vessels not in contact (%) = 28

#8



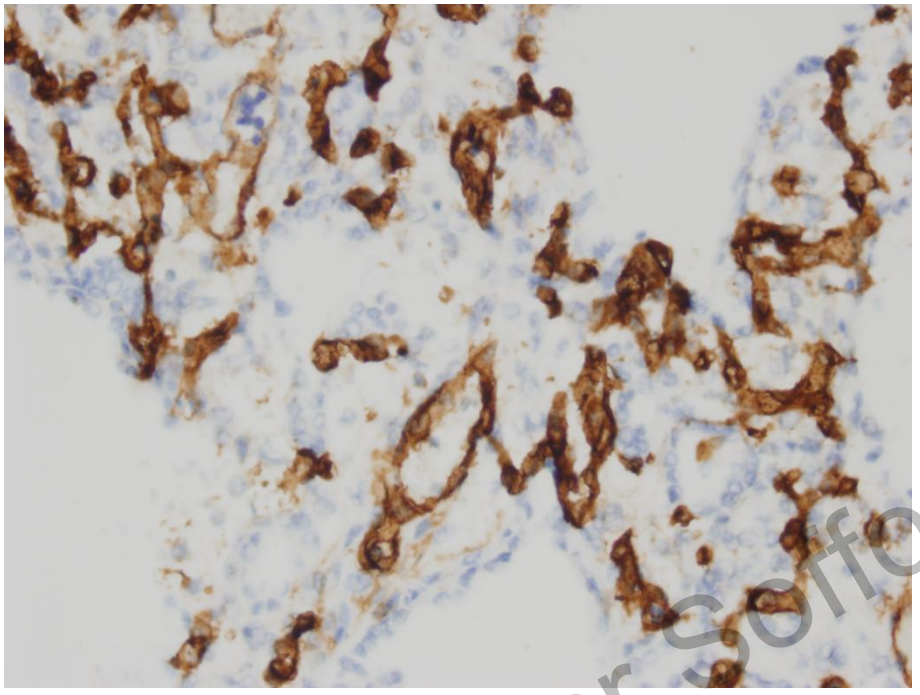


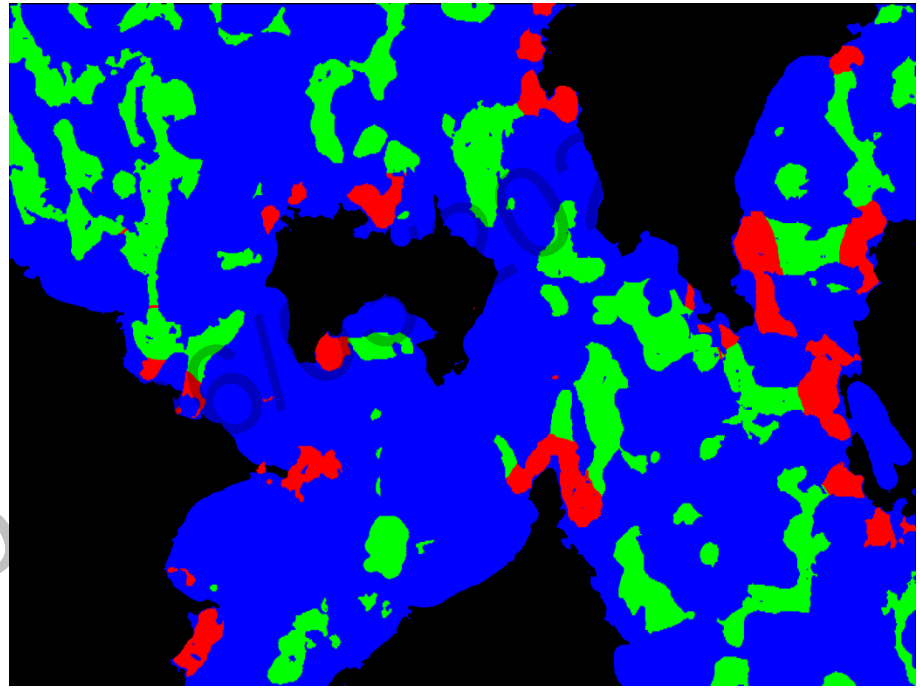
Interstitium/airspaces = 1.2

Vessels/interstitium (%) = 51

Vessels not in contact (%) = 17

#9



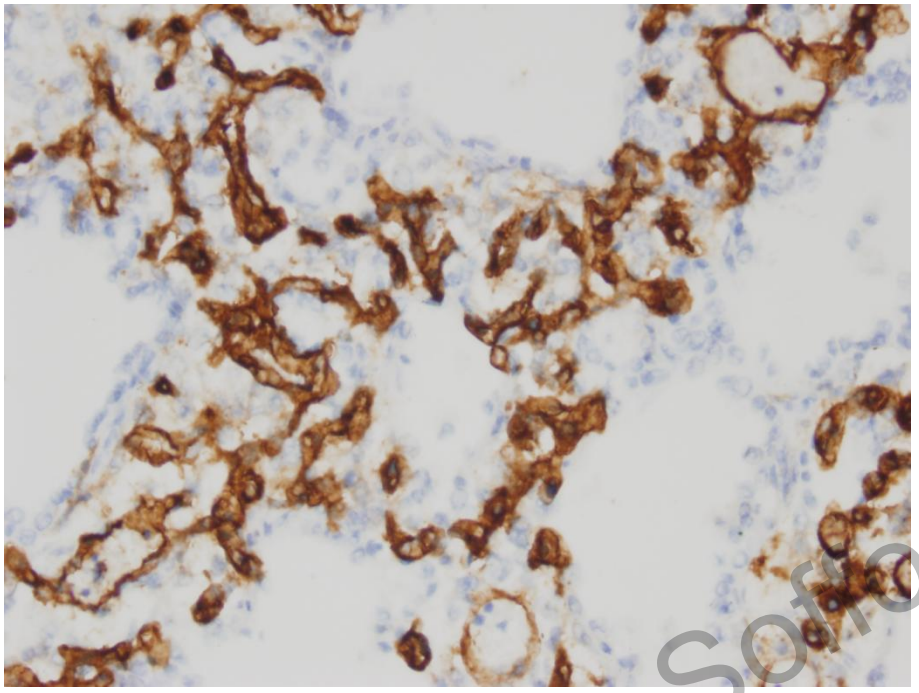


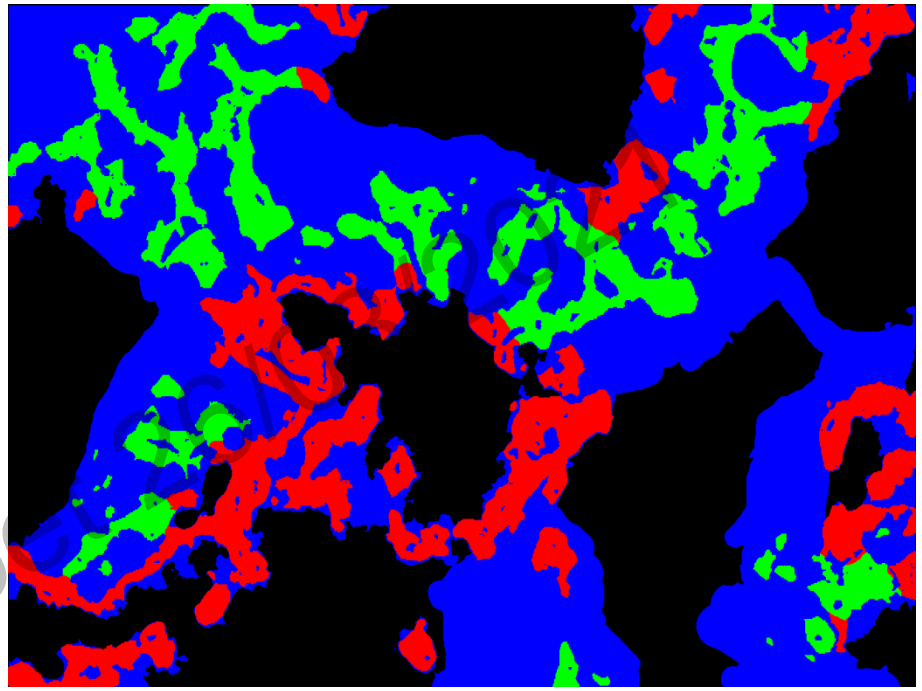
Interstitium/airspaces = 2.5

Vessels/interstitium (%) = 23

Vessels not in contact (%) = 80

#10





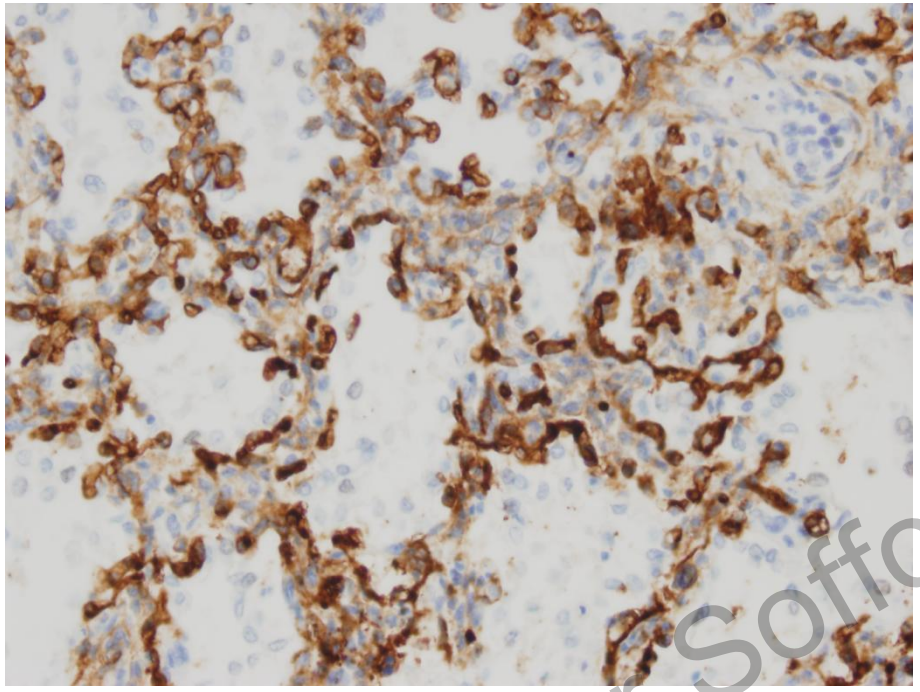
Interstitium/airspaces = 1.8

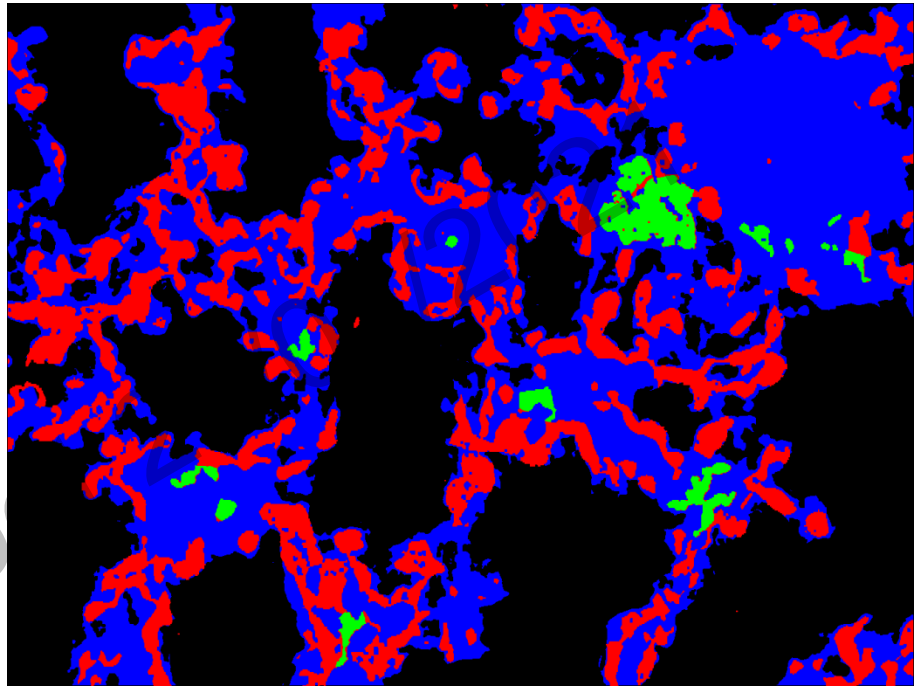
Vessels/interstitium (%) = 35

Vessels not in contact (%) = 40

Control

#1



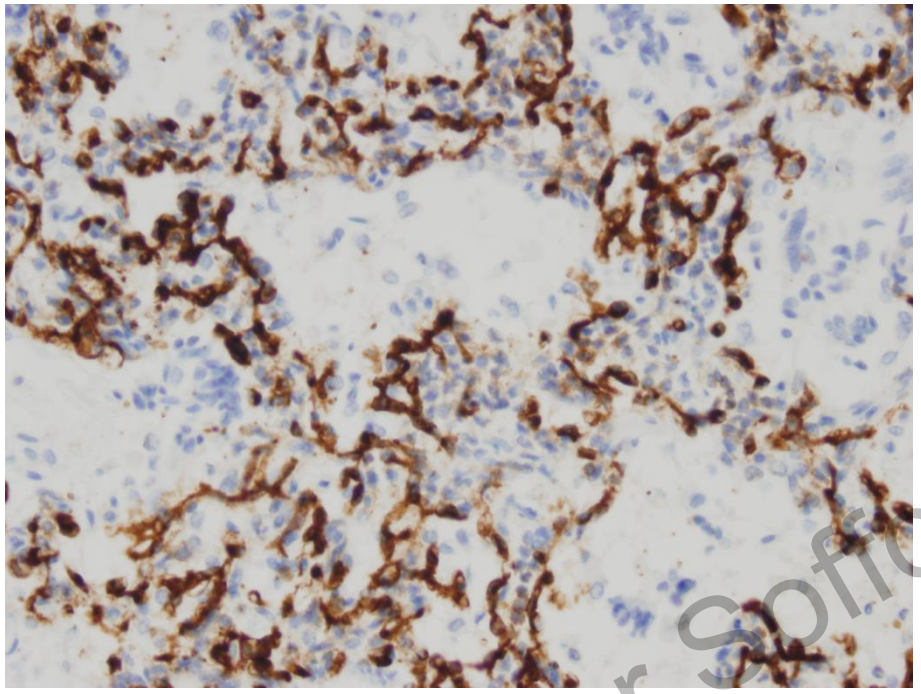


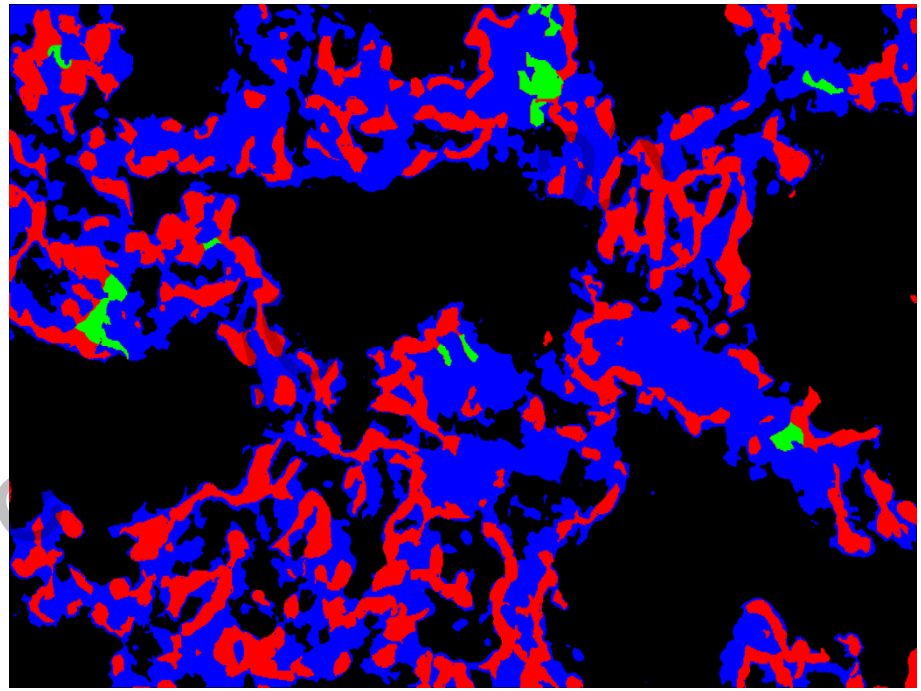
Interstitium/airspaces = 1.2

Vessels/interstitium (%) = 33

Vessels not in contact (%) = 7

#3



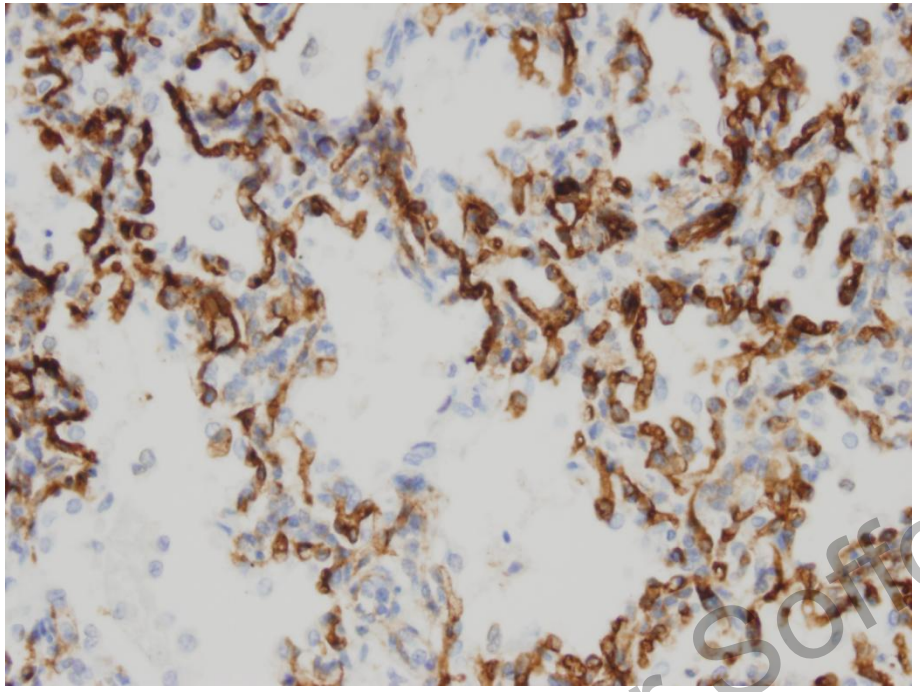


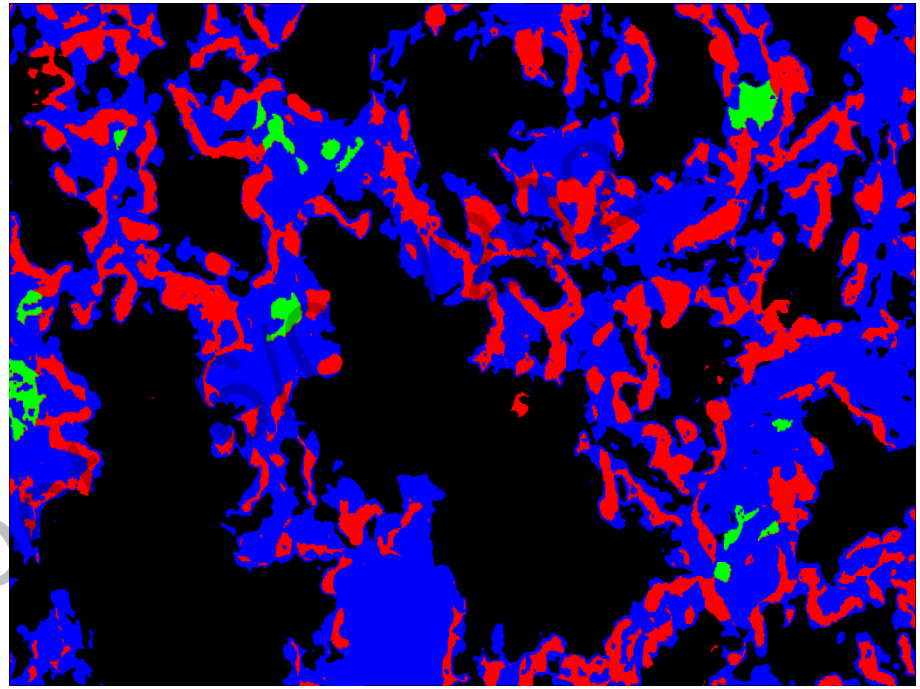
Interstitium/airspaces = 0.97

Vessels/interstitium (%) = 35

Vessels not in contact (%) = 4

#4



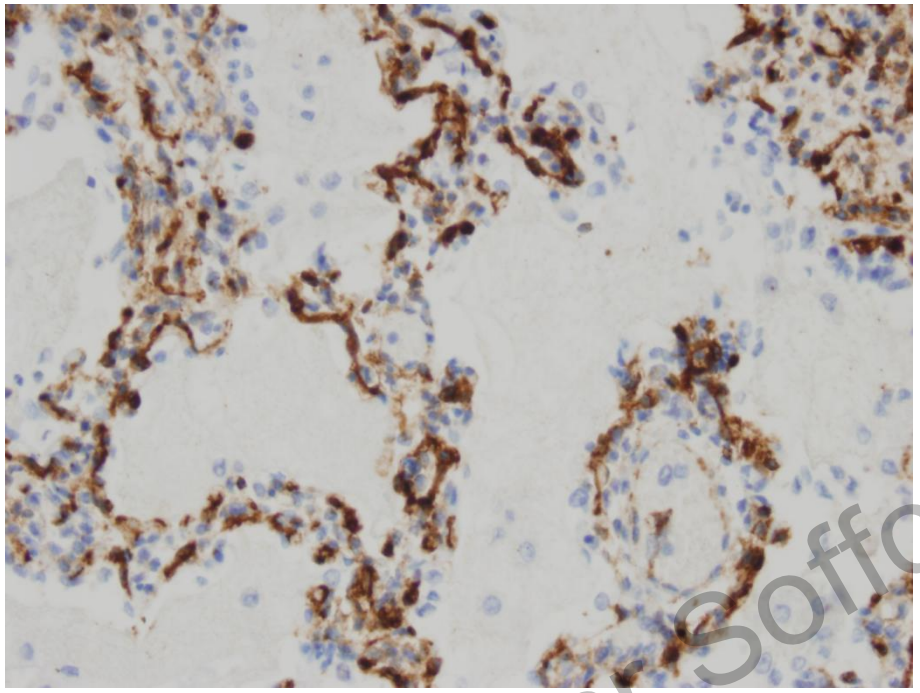


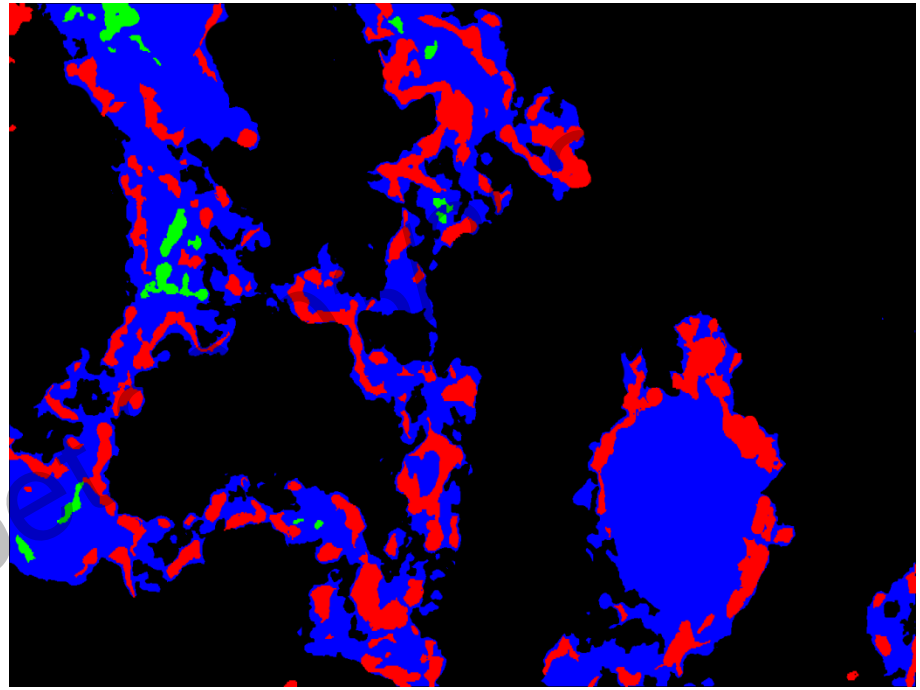
Interstitium/airspaces = 1.1

Vessels/interstitium (%) = 31

Vessels not in contact (%) = 6

#6



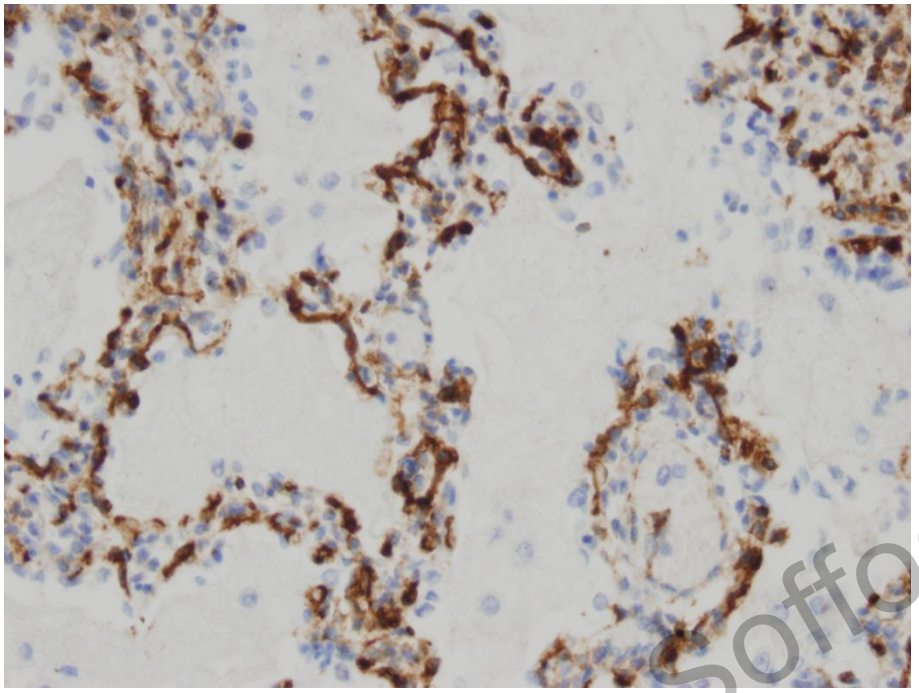


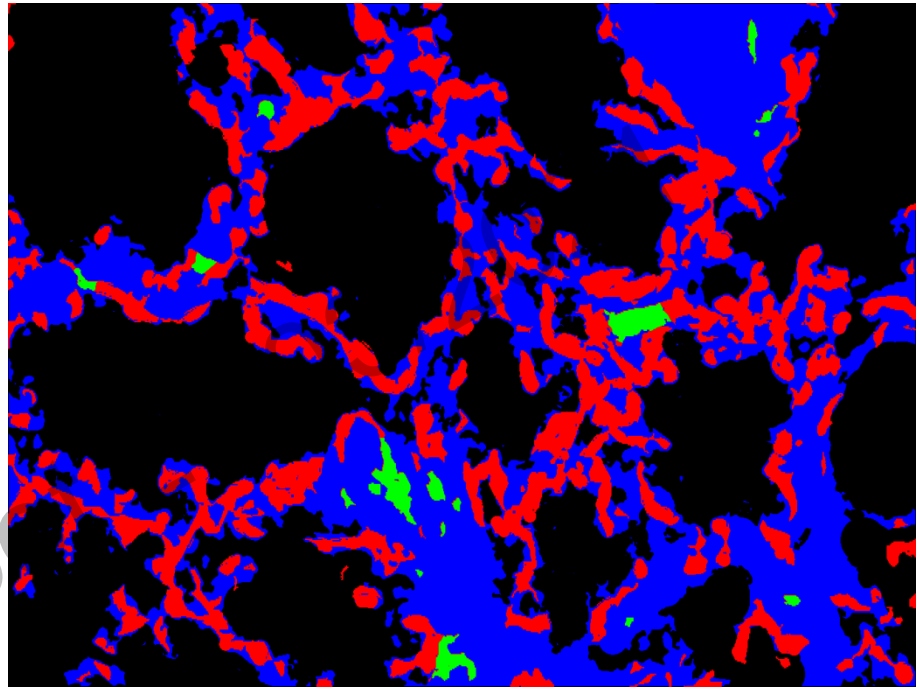
Interstitium/airspaces = 0.6

Vessels/interstitium (%) = 22

Vessels not in contact (%) = 8

#10



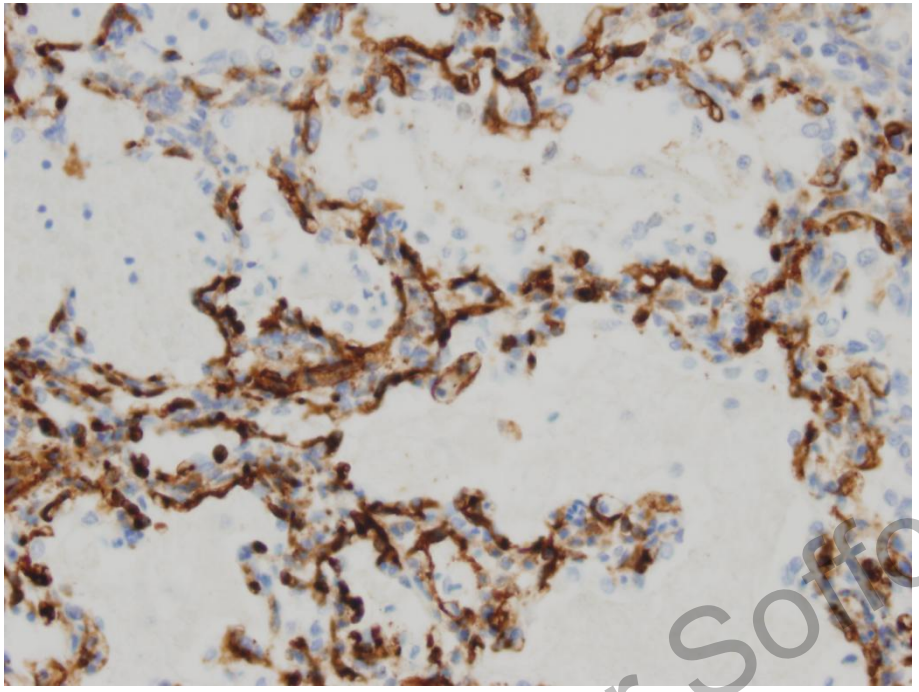


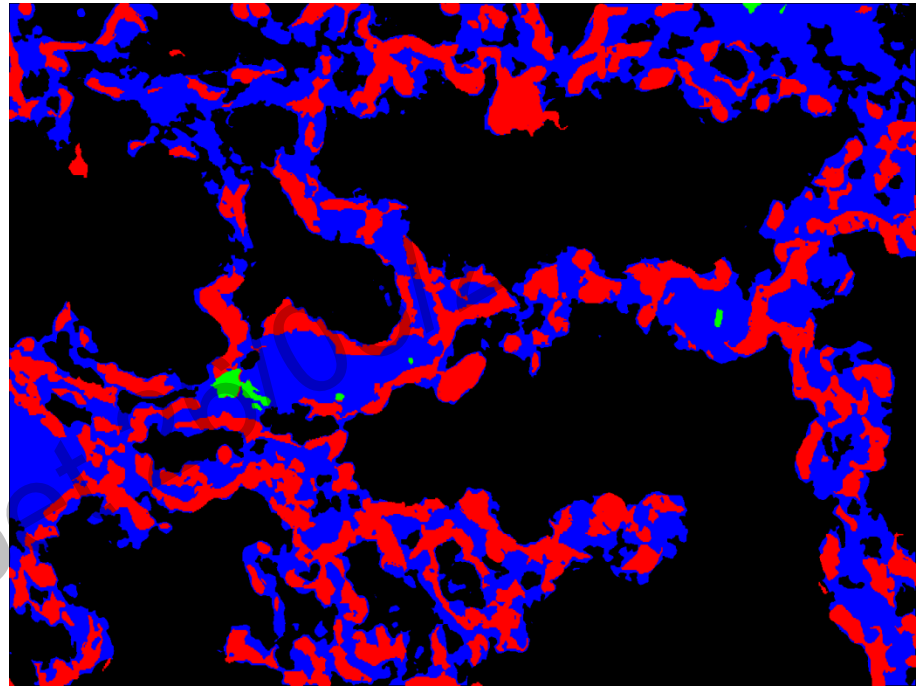
Interstitium/airspaces = 0.88

Vessels/interstitium (%) = 35

Vessels not in contact (%) = 5

#11



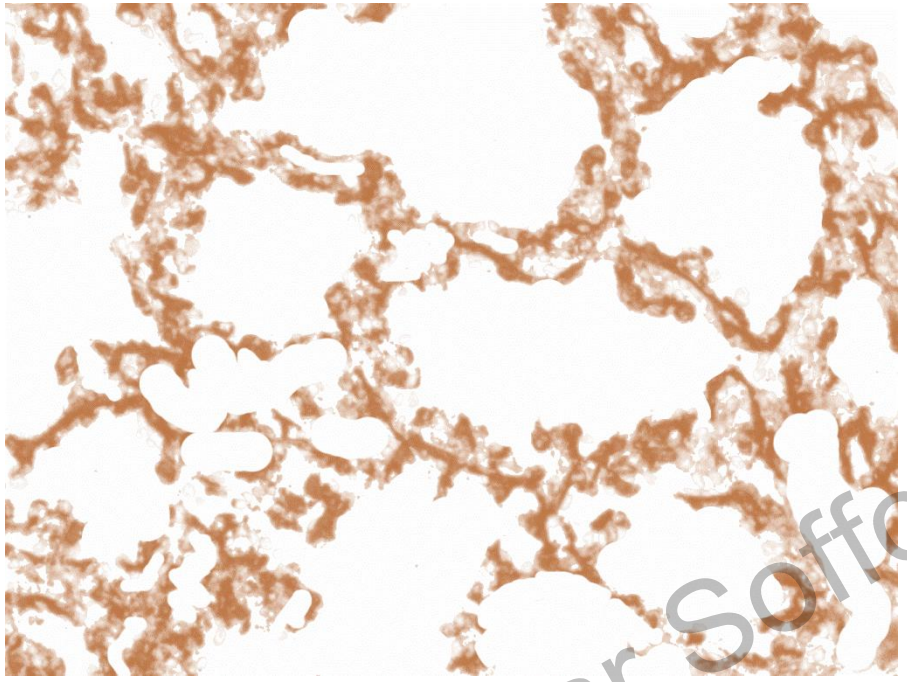


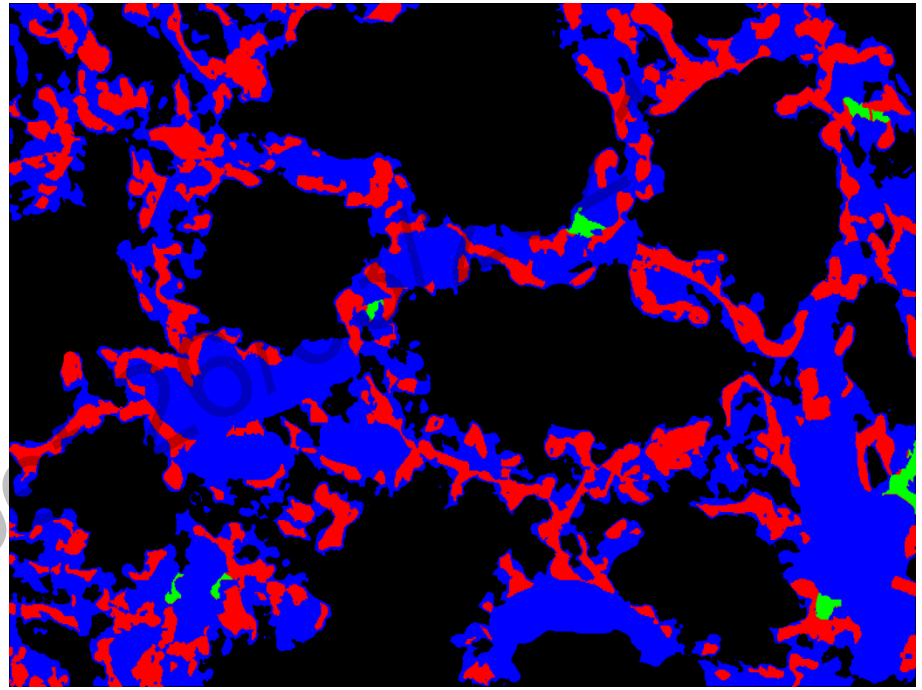
Interstitium/airspaces = 0.74

Vessels/interstitium (%) = 38

Vessels not in contact (%) = 1

#12





Interstitium/airspaces = 0.9

Vessels/interstitium (%) = 31

Vessels not in contact (%) = 2

Just how strong is the proof that capillary depletion in ADC exists?

The statement that capillary depletion in ADC exists is often repeated but is actually (very) weak

Several statements about capillary morphology in ACD

- ***Towe et al. J Pediatr. 2018;194: 158–64***
  - abnormal (but not diminished) capillarization
- ***Kitano et al. Diagnostic Pathology 2020; 15: 48***
  - diminution of capillary numbers “not remarkable”
  - unusual glomeruloid endothelial proliferation
- ***Alturkustani et al. Cardiovasc Pathol. 2021; 50: 107289.***
  - 15 out of 16 cases showed a variable degree of aberrant alveolar septal microvascular proliferation.
- ***Hull J, Forton J, Thomson A. Paediatric Respiratory Medicine. Oxford University Press, 2015.***
  - paucity of capillaries adjacent to alveolar epithelial cells (but not of capillaries in general)

Histopathology 2008, **53**, 450–457. DOI: 10.1111/j.1365-2559.2008.03134.x

Capillary apposition and density in the diagnosis of alveolar capillary dysplasia n = 6

L Melly, N J Sebire,[1] M Malone[1] & A G Nicholson[2]
Departments of Histopathology, Royal Free Hospital, [1]Great Ormond Street Hospital and [2]Royal Brompton Hospital, London, UK

Table 1. Histological parameters scored in a semiquantitative fashion

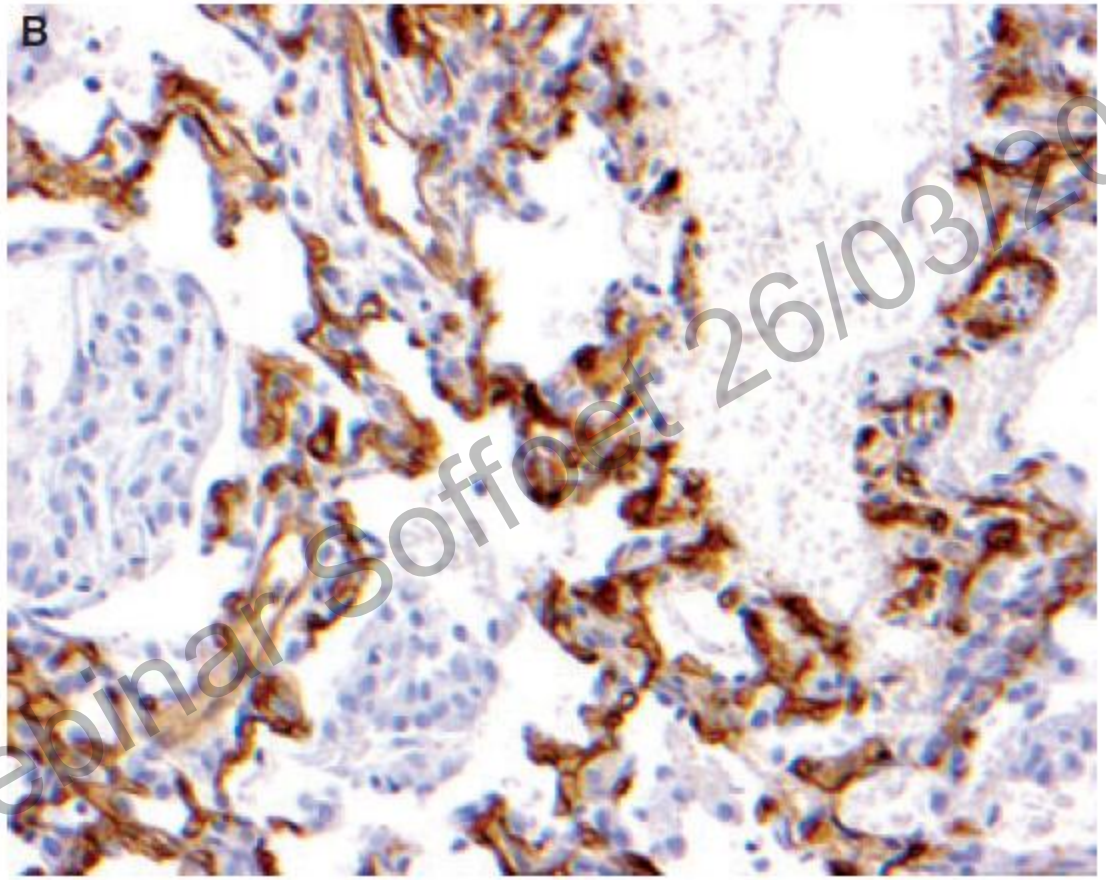
Misalignment of veins: present (2), probably present (1), absent (0)
Septal development: normal/abnormal
Presence of clear cells in interstitium [0 (absent)–6 (abundant)]
Presence of type 2 cell hyperplasia [0 (absent)–6 (marked)]
Evidence of PAH in preacinar arteries [0 (absent)–6 (marked)]
Evidence of PAH in intra-acinar arteries [0 (absent)–6 (marked)]
Capillary density [0 (absent)–6 (normal)]
Capillary apposition [0 (absent)–6 (normal)]

Weak proof:

No controls!

Using semiquantitative scores is clumsy

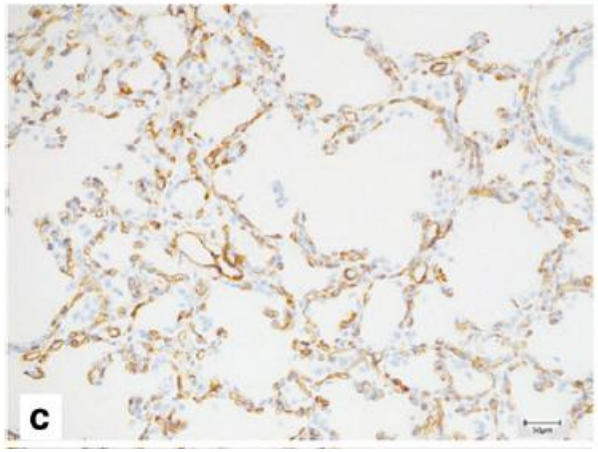
How does one assess capillary density (counts) in images like this?

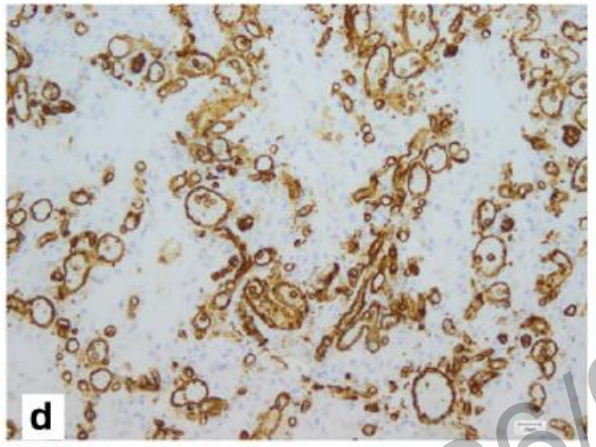


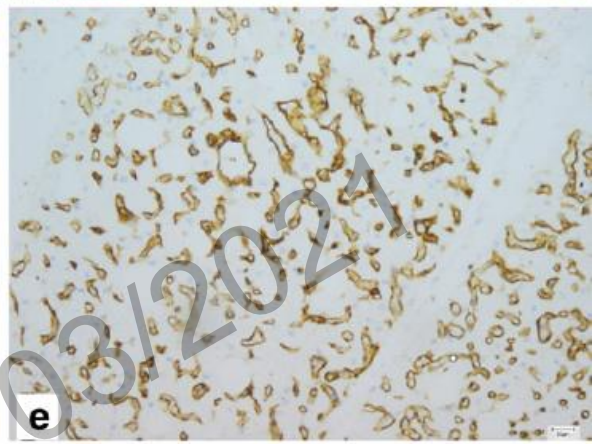
Melly et al. Histopathology 2008, 53, 450–57

CD34

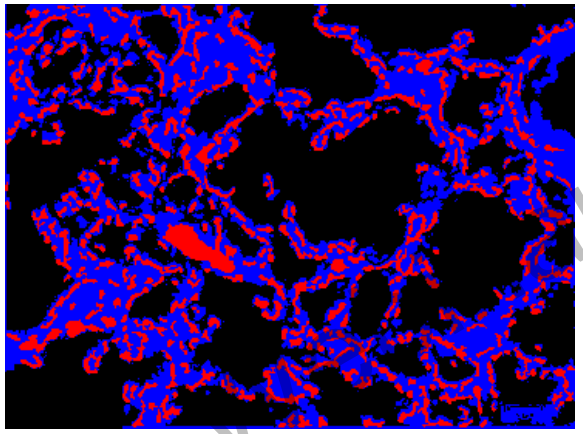
vessel area / interstitial area %





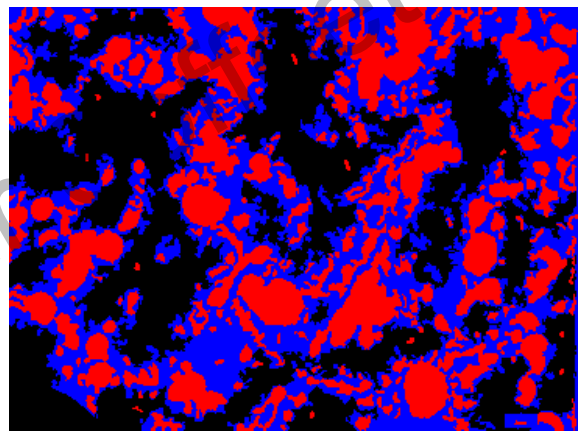


control



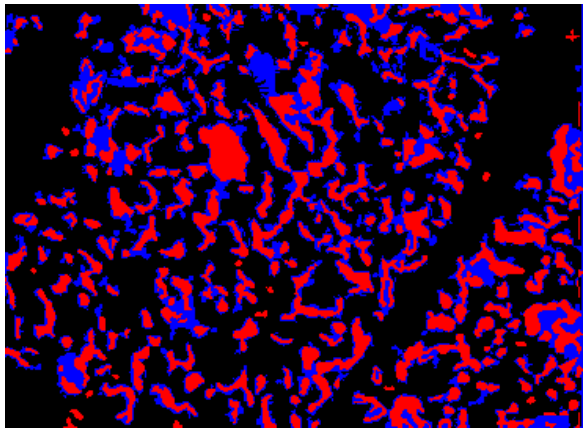
32 %

ACD patient 1



47 %

ACD patient 2



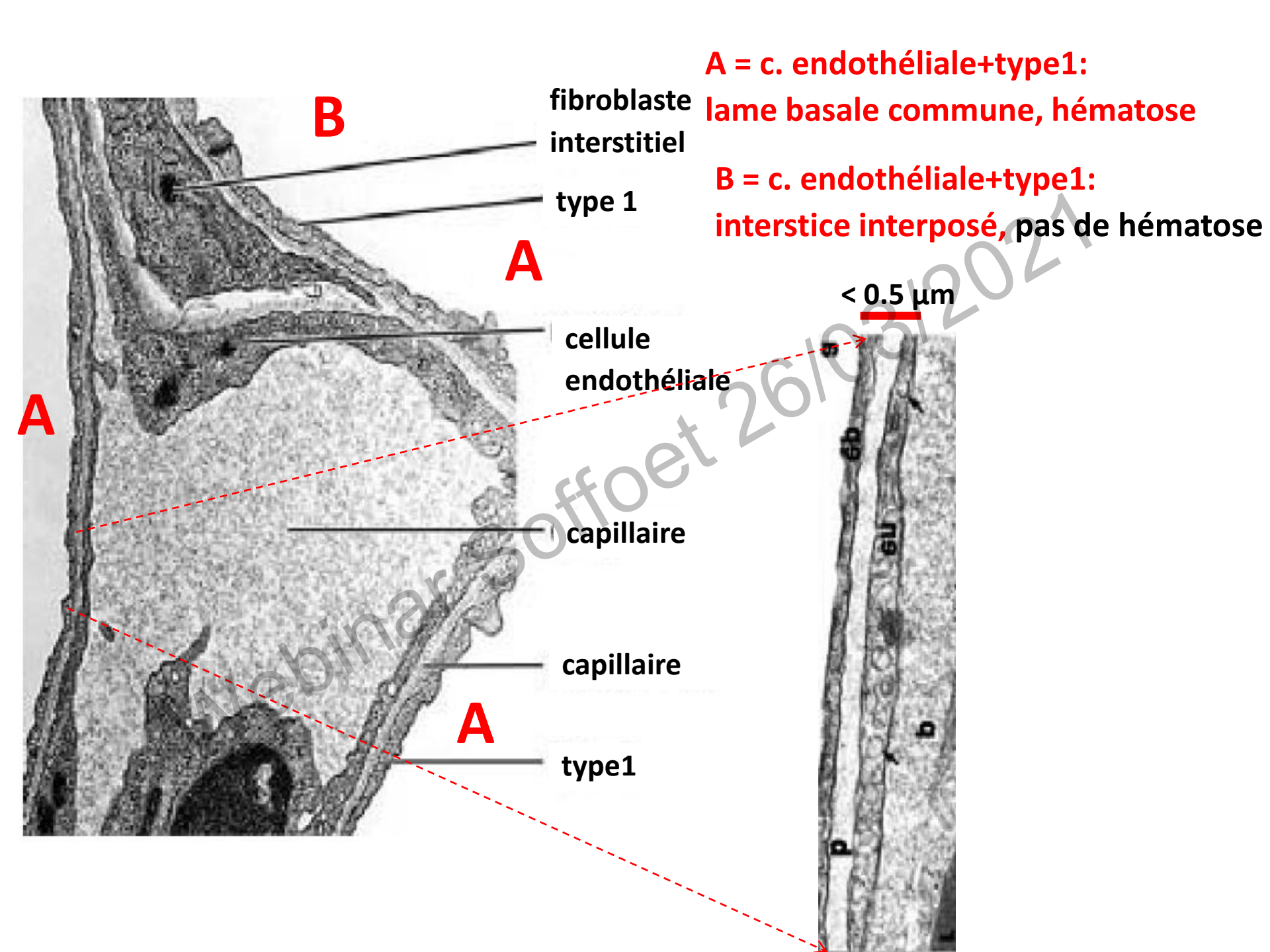
53 %

Kozlowska et al. BMC Pediatrics 2020; 20: 320.

A disproof !

Conclusions (weak :) only 2 cases

- the compromised air / blood barrier seems to be the most prominent histological feature of ADC; as a reminder, see next 2 slides: normally, it is < 500 nm thick
- capillary density seems to be augmented rather than diminished
- and is more compatible with dysplasia rather than with hypoplasia
- 1st ever detailed morphometric study of interstitial lesions in ACD


A = c. endothéliale+type1:
lame basale commune, hématose
B = c. endothéliale+type1:
interstice interposé, pas de hématose
B
fibroblaste
interstitiel
type 1
A
< 0.5 µm
cellule
endothéliale
A
capillaire
capillaire
A
type1
6b
6u
b
p
Webinar Soffoet 26/03/2021

La barrière air/sang a 3 composantes qui permettent l'hématose

1 type 1 pneumocyte

2 common basal membrane

3 endothelial cell cytoplasm