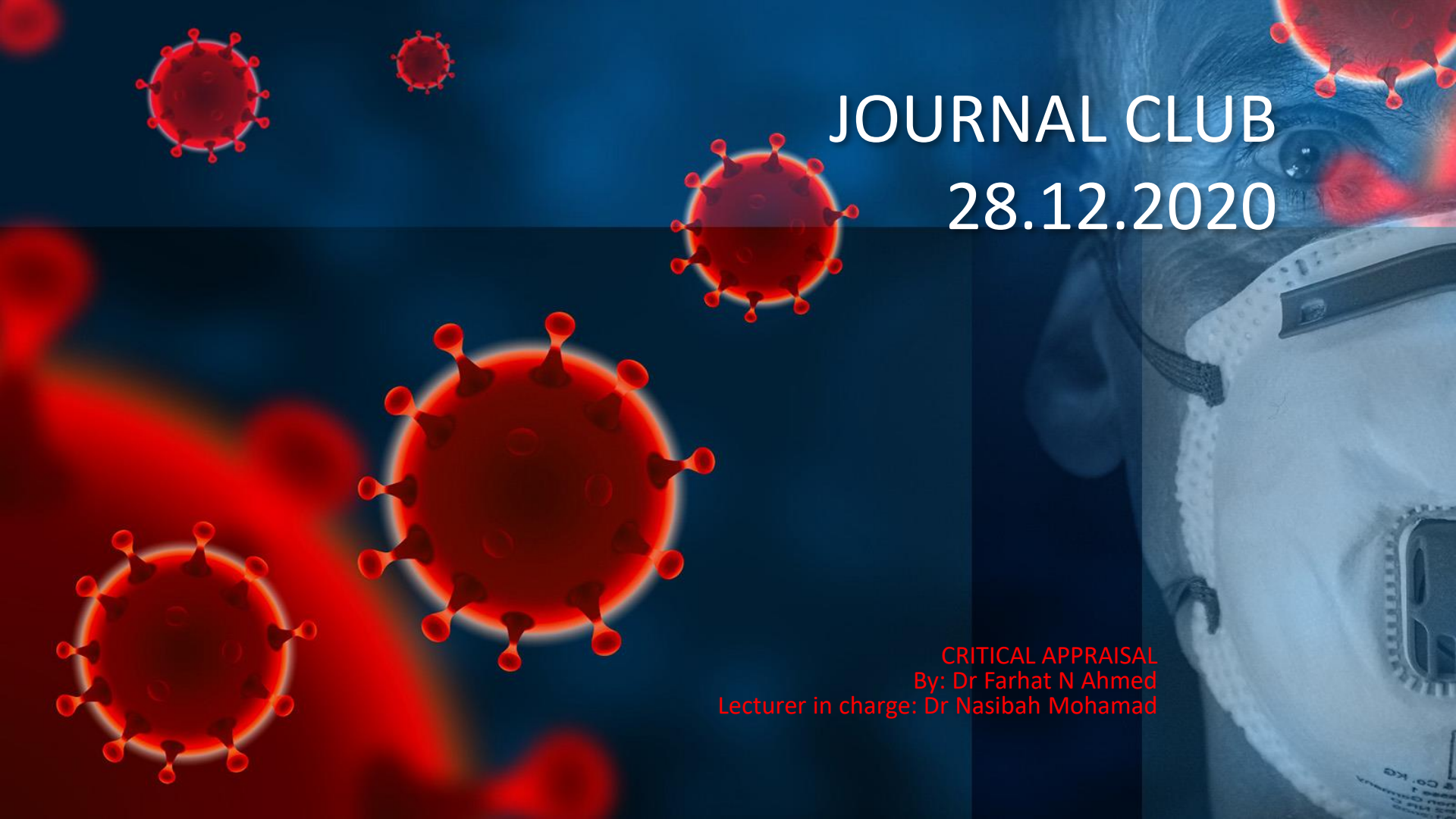
JOURNAL CLUB
28.12.2020

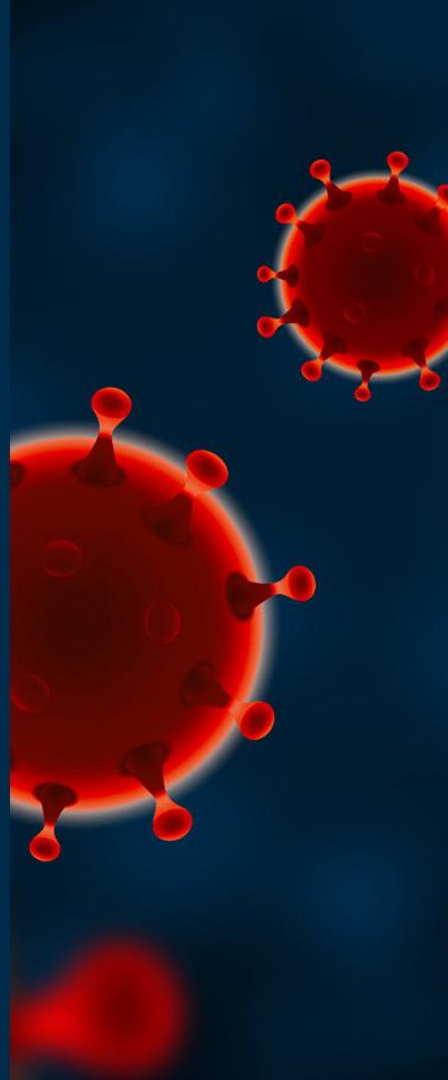


CRITICAL APPRAISAL

By: Dr Farhat N Ahmed
Lecturer in charge: Dr Nasibah Mohamad

Pulmonary Angiopathy in Severe COVID-19: Physiologic, Imaging, and Hematologic Observations

- CRITICAL APPRAISAL



ORIGINAL ARTICLE

Pulmonary Angiopathy in Severe COVID-19: Physiologic, Imaging, and Hematologic Observations

Brijesh V. Patel[1,2*], Deepa J. Arachchillage[3,4*], Carole A. Ridge[5,6*], Paolo Bianchi[7], James F. Doyle[7], Benjamin Garfield[7], Stephane Ledot[7], Cliff Morgan[7], Maurizio Passariello[7], Susanna Price[5,7], Suveer Singh[1,7], Louit Thakuria[7], Sarah Trenfield[7], Richard Trimlett[7], Christine Weaver[7], S. John Wort[5,8], Tina Xu[7], Simon P. G. Padley[5,6*], Anand Devaraj[5,6*], Sujal R. Desai[5,6*], and The Severe Acute Respiratory Failure Service and The Departments of Anaesthesia and Critical Care, Royal Brompton Hospital

[1]Division of Anaesthetics, Pain Medicine, and Intensive Care, Department of Surgery and Cancer, [3]Centre for Haematology, Department of Immunology and Inflammation, and [4]National Heart and Lung Institute, Imperial College London, London, United Kingdom; [2]Department of Adult Intensive Care, [5]Department of Haematology, [6]Department of Radiology, [7]Department of Adult Intensive Care, and [8]The Pulmonary Hypertension Service, Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom

ORCID IDs: 0000-0002-5573-2503 (B.V.P.); 0000-0001-5993-4850 (D.J.A.); 0000-0003-2510-5856 (C.A.R.); 0000-0001-9973-9283 (P.B.); 0000-0002-7060-0373 (J.F.D.); 0000-0001-9261-3186 (S.L.); 0000-0002-6425-3360 (S.P.); 0000-0003-3219-8966 (S.S.); 0000-0003-1298-6578 (L.T.); 0000-0002-7023-8044 (C.W.); 0000-0003-4287-1173 (S.J.W.); 0000-0002-7381-2339 (S.P.G.P.); 0000-0002-5237-3613 (S.R.D.).

Abstract

Rationale: Clinical and epidemiologic data in coronavirus disease (COVID-19) have accrued rapidly since the outbreak, but few address the underlying pathophysiology.

Objectives: To ascertain the physiologic, hematologic, and imaging basis of lung injury in severe COVID-19 pneumonia.

Methods: Clinical, physiologic, and laboratory data were collated. Radiologic (computed tomography (CT) pulmonary angiography [$n = 39$] and dual-energy CT [DECT, $n = 20$]) studies were evaluated: observers quantified CT patterns (including the extent of abnormal lung and the presence and extent of dilated peripheral vessels) and perfusion defects on DECT. Coagulation status was assessed using thromboelastography.

Measurements and Results: In 39 consecutive patients (male: female, 32:7; mean age, 53 ± 10 yr [range, 29–79 yr]; Black and minority ethnic, $n = 25$ [64%]), there was a significant vascular perfusion abnormality and increased physiologic dead space (dynamic compliance, 33.7 ± 14.7 ml/cm H_2O; Murray lung injury score, 3.14 ± 0.53; mean ventilatory ratios, 2.6 ± 0.8) with evidence of hypercoagulability and fibrinolytic "shutdown". The mean CT extent (±SD) of normally aerated lung, ground-glass opacification, and dense parenchymal opacification were 23.5 ± 16.7%, 36.3 ± 24.7%, and 42.7 ± 27.1%, respectively. Dilated peripheral vessels were present in 21/33 (63.6%) patients with at least two assessable lobes (including 10/21 [47.6%] with no evidence of acute pulmonary emboli). Perfusion defects on DECT (assessable in 18/20 [90%]) were present in all patients (wedge-shaped, $n = 3$; mottled, $n = 9$; mixed pattern, $n = 6$).

Conclusions: Physiologic, hematologic, and imaging data show not only the presence of a hypercoagulable phenotype in severe COVID-19 pneumonia but also markedly impaired pulmonary perfusion likely caused by pulmonary angiopathy and thrombosis.

Keywords: novel coronavirus disease 2019; acute respiratory distress syndrome; pulmonary perfusion; thoracic imaging; mechanical ventilation

(Received in original form April 27, 2020; accepted in final form July 14, 2020)

*These authors contributed equally to this work.

A list of members of the Severe Acute Respiratory Failure Service and the Departments of Anesthesia and Critical Care is provided in the online supplement.

Author Contributions: Study concepts and design: B.V.P., D.J.A., C.A.R., S.P.G.P., A.D., and S.R.D. Literature review: B.V.P., D.J.A., C.A.R., S.P.G.P., A.D., and S.R.D. Clinical data collection: all authors. Manuscript preparation/editing: B.V.P., D.J.A., C.A.R., S.P.G.P., A.D., and S.R.D. Data analysis: B.V.P., D.J.A., C.A.R., S.P.G.P., A.D., and S.R.D. Statistical analysis: B.V.P., C.A.R., and A.D. Final manuscript review: all authors.

Correspondence and requests for reprints should be addressed to Brijesh V. Patel, M.D., Ph.D., Division of Anaesthetics, Pain Medicine, and Intensive Care and Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, and Department of Adult Intensive Care, The Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, London SW3 6NP, UK. E-mail: brijesh.patel@imperial.ac.uk.

This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 202, Iss 5, pp 690–699, Sep 1, 2020

Originally Published in Press as DOI: 10.1164/rccm.202004-1412OC on July 15, 2020
Internet address: www.atsjournals.org

TITLE

Pulmonary Angiopathy in Severe COVID-19: Physiologic, Imaging, and Hematologic Observations

- Recent publication
- High impact journal (17.45)
- Original article
- Title clearly describes the study

RATIONALE

The global spread of coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was classified a pandemic by the World Health Organization in March 2020.

Respiratory failure is the dominant cause of death, and current management of COVID-19 centers on supportive care.

The other major issue in COVID-19 is the fundamental role of endothelial injury and disrupted vasoregulation. The latter has been proposed as a key component in early COVID-19–related ARDS.

PROBLEM STATEMENT

Objectives: To ascertain the physiologic, hematologic, and imaging basis of lung injury in severe COVID-19 pneumonia.

Few have addressed and researched the underlying pathophysiology

Methods

- Retrospective, observational study
- 39 consecutive mechanically ventilated patient confirmed SARS-CoV-2 infection
- between 17 March to 10 April 2020
- For CT interpretation two observers (both thoracic radiologists of 14 and 24 years' experience, respectively)
- Pulmonary blood volume images acquired using DECT were reviewed by two thoracic radiologists (14 and 30 years' experience,respectively)

VALIDITY:

Panels for imaging are experienced radiologists.

Inclusion criteria:

- Laboratory-confirmed positive for COVID-19

- Patient were mechanically ventilated or on ECMO with active COVID-19-induced respiratory failure

- Had undergone CTPA including DECT (where feasible)

Exclusion criteria

No exclusion criteria mentioned in the study

Impacts of exclusion criteria related to comorbidities that could bias the results:
On the basis of the inclusion and exclusion criteria, we can make a judgment regarding their impact on the external validity of the results. Making those judgments require in-depth
knowledge of the area of research, as well as of in what direction each criterion could affect the external validity of the study.*

For example: in this article there may be dual pathologies at play in critically ill patients, namely,
acute PE from DVT and a widespread pulmonary angiopathy.

* Patino CM, Ferreira JC. Inclusion and exclusion criteria in research studies: definitions and why they matter. *J Bras Pneumol*. 2018;44(2):84. doi:10.1590/s1806-37562018000000088

Data collection

- Demographic, clinical, laboratory and treatment data were extracted from electronic medical records and a point-of-care database.
- Respiratory physiology measurement are presented as on admission and shortly before CT-scan imaging.
- All data were reviewed and collated by investigating physicians.

Laboratory procedures

SARS-CoV-2 infection was confirmed on real-time PCR assay

Routine blood investigation:

- Complete blood count
- Coagulation profile* [assess using thromboelastography (TEG 6; Haemonetics)]
- Serum biochemical test (including RFT and LFT, LDH and electrolytes)
- Myocardial enzymes
- Serum ferritin

The frequency of investigations and further tests were determined by the treating physician.

CT image acquisition and interpretation

The incidence of venous thrombosis was confirmed by review of reports of lower and upper limb compression ultrasound and/or CT venography where available.

Two observers (both thoracic radiologists of 14 and 24 years experience, respectively), reviewed all available CT studies by component of abnormal lung were visually quantified.

The presence of peripheral dilated (branching and tortuous) vessels in the lung not obscured by DPO was recorded.

Pulmonary blood volume images acquired using DECT were reviewed by two thoracic radiologists (4 and 30 years experience, respectively).

The evaluation for the presence/absence of perfusion defects and, when present, categorized as wedge-shaped, mottled, or mixed based on appearances described in chronic thromboembolic disease.

APPROPRIATE
For imaging data collection

Statistical analysis

1. Descriptive statistic – summarized data; results reported as medians and interquartile ranges or means and SD
2. Categorical variables – summarize as counts and percentages.
3. Statistical analyses were performed using GraphPad Prism v8.4 (GraphPad Software).
   - Normality for continuous variables was tested with the D'Agostino and Pearson normality test.
   - Two-tailed t test, Mann-Whitney U test, or Kruskal-Wallis test with Dunn's multicomparison was used to compare differences between groups where appropriate.
   - Correlation performed using Spearman correlation coefficient and nonlinear least squares regression fitting.

Need more elaboration

APPROPRIATE

RESULTS

Demographics and Clinical Characteristics	Number (%), Median (Range), or Mean (±SD)
Age	52.5 (29–79)
Sex, M	32 (82)
Sex, F	7 (18)
White	14 (36)
Black and minority ethnic	25 (64)
BMI, kg/m^2	31.3 (±6.1)
BMI > 30 kg/m^2	22 (57)
Diabetes mellitus	8 (21)
Hypertension	15 (39)
Asthma	3 (8)
Hyperlipidemia	2 (5)
Physiologic characteristics (on admission)	
Pa_{O_2}/Fi_{O_2}	114.9 (±74.2)
Pa_{CO2}, mm Hg	63.6 (±20.6)
Minute ventilation, L/min	11.7 (±2.2)
Dynamic compliance, ml/cm H_2O	33.7 (±14.7)
Positive end-expiratory pressure, cm H_2O	12.3 (±2.4)
Murray lung injury score	3.14 (±0.53)
Ventilatory ratio	2.6 (±0.8)
Admission sequential organ failure score	8.0 (±2.5)
Admission APACHE II score	18.7 (±5.0)
Respiratory ECMO survival prediction score	3.4 (±1.9)
Laboratory tests on admission (normal values)	
White cell count, ×10^9/L (3.6–11.0)	10.6 (±4.4)
Neutrophils, ×10^9/L (1.8–7.5)	9.3 (±4.3)
Lymphocytes, ×10^9/L (1.0–4.0)	0.76 (±0.4)
Creatinine, μmol/L (45–110)	172 (±141)
CRP, mg/L (<3)	305 (±101)
Ferritin, ng/ml (18–270)	987 (552–1,425)
Lactate dehydrogenase, U/L (<250)	996 (773–1,270)
Platelets, 10^9/L (146–360)	272 (±77)
Fibrinogen, g/L (1.5–4.5)	6.6 (±1.9)
Antithrombin 3, IU/dl (70–140)	70.6 (±23.7)
APTT, s (26–36)	38.8 (±13.1)
PT, s (10–12.5)	14.1 (±2.1)
D-dimer, ng/ml (208–318)	6,440 (±10,434)
High-sensitivity troponin, ng/L (<14)	143 (±262)
Brain natriuretic peptide, ng/L (<100)	186 (±274)

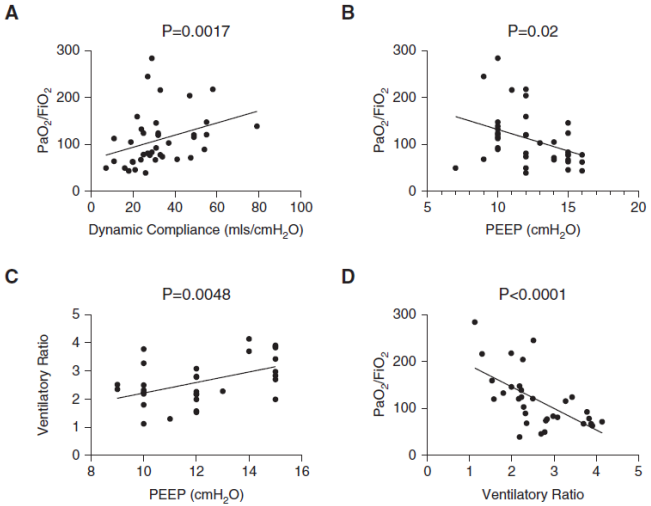
Definition of abbreviations: APACHE = The Acute Physiology and Chronic Health Evaluation; APTT = activated partial thromboplastin time; BMI = body mass index; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; PT = prothrombin time.

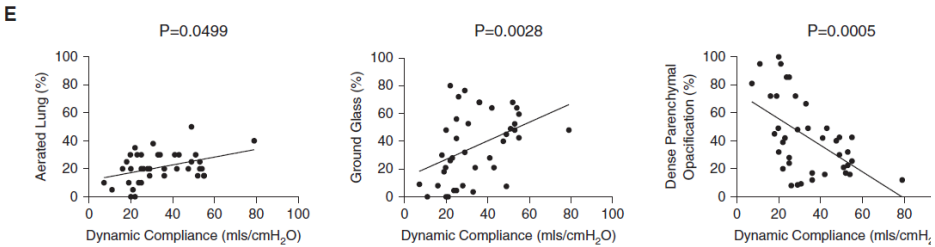
Table 2. Computed Tomography Abnormalities in 39 Mechanically Ventilated Patients with Severe COVID-19 Pneumonia

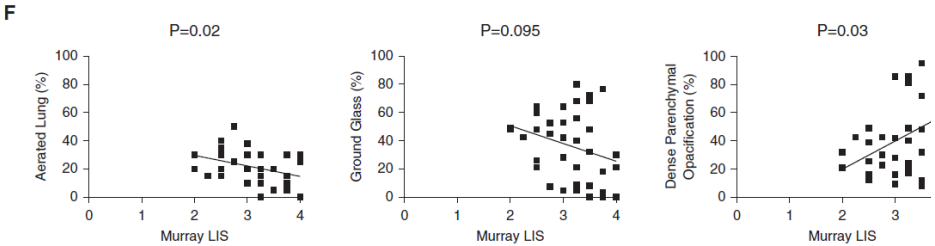
Computed Tomography Findings	All (*N* = *39*)
Aerated lung, %	23.5 (±16.7)
Ground-glass opacity, %	36.3 (±24.7)
Dense parenchymal opacification, %	42.7 (±27.1)

	Number of Patients	Proportion (%)
Pulmonary embolism	15	15/39 (38.5)
Dilated peripheral vessels	21	21/33* (63.6)
1–5 segments	14	14/21 (66.7)
6–10 segments	7	7/21(33.3)
>10 segments	0	0/21 (0)
Dilated peripheral vessels without PE	10	10/21 (47.6)
Perfusion defect present	18	18/18† (100)
1–5 segments	14	14/18 (77.8)
6–10 segments	4	4/18 (22.2)
>10 segments	0	0/18
Perfusion defects without PE	8	8/18 (44.4)
DECT perfusion defect morphology		
Wedge shaped	3	3/18 (16.7)
Mottled	9	9/18 (50)
Mixed pattern	6	6/18 (33.3)
Deep venous thrombosis	4	4/22‡ (18.2)

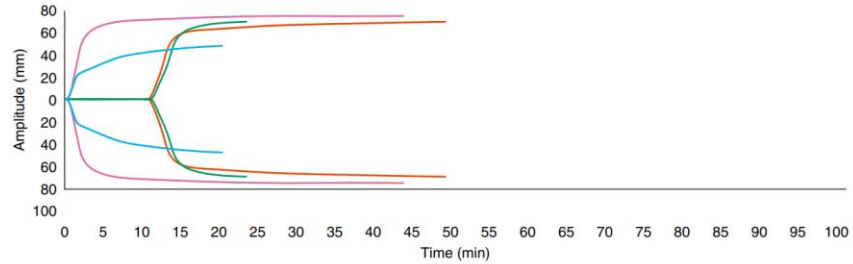
Definition of abbreviations: COVID-19 = coronavirus disease; DECT = dual-energy computed tomography; PE = pulmonary embolism.
*Of 39 patients, 33 had at least two assessable lobes not obscured by dense collapse or consolidation.
†Of 20 patients, 18 had at least two assessable lobes on pulmonary blood volume color maps.
‡Twenty-two patients underwent peripheral limb ultrasound or computed tomography venography.





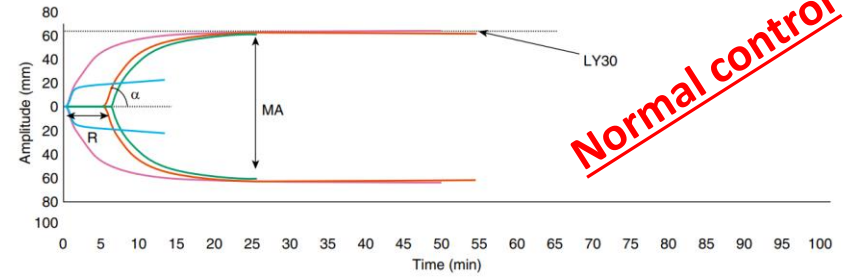


A



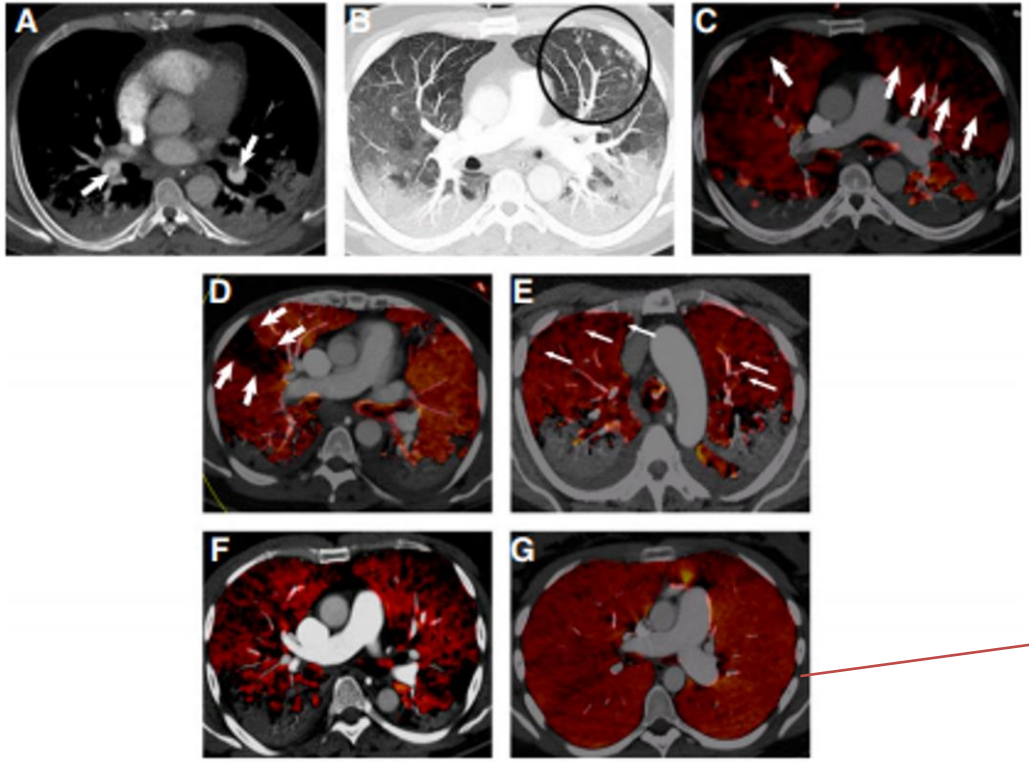
	TEG–ACT (sec)	R (min)	K (min)	ANGLE (deg)	A10 (mm)	MA (mm)	LY30 (%)
CK		11.0	1.2	77.5		62.7	0.0
		4.6 – 9.1	0.8 – 2.1	63 – 78		52 – 69	0..0 – 2.6
CRT	106.6	0.6	0.7	81.6	72.4	73.4	0.0
	82 –152	0.3 –1.1	0.8 –2.7	60 –78	44 –67	52 – 70	0.0 – 2.2
CKH		11.3	1.3	75.7		70.6	
		4.3 – 8.3	0.8 – 1.9	64 – 77		52.69	
CFF					43.2	48.5	
					15 – 30	15 – 32	

B



Normal control

	TEG–ACT (sec)	R (min)	K (min)	ANGLE (deg)	A10 (mm)	MA (mm)	LY30 (%)
CK		5.4	1.1	74.5		62.6	0.1
		4.6 – 9.1	0.8 – 2.1	63 – 78		52 – 69	0.0 – 2.6
CRT	97.3	0.5	1.0	77.0	58. 1	63.1	0.0
	82 – 152	0.3 – 1.1	0.8 – 2.7	60 – 78	44 – 67	52 – 70	0.0 – 2.2
CKH		6.2	1.2	73.3		61.5	
		4.3 – 8.3	0.8 – 1.9	64 – 77		52 – 69	
CFF					22.2	23.0	
					15 – 30	15 – 32	



Good images with description and videos for future references but only describe the obvious findings in severe cases.

Normal study used for reference.

CONCLUSIONS

LIMITATIONS

- Small sample size and a single institution study.
- Retrospective observational nature with absence of matched (non–COVID-19) controls.
- Lack of a validation cohort.
- Focus on patients with severe COVID-19–induced respiratory failure.

SUGGESTIONS:

Future studies comparing a matched control group of patients with non–COVID-19–related ARDS are clearly necessary to ascertain whether the imaging findings reported herein are truly related to SARS-CoV-2. Progression of disease can be better understood if only severe patients were not the only ones focused on for the study.

CONCLUSIONS

Overall:

- It is the first to systematically evaluate on pulmonary angiopathy involving multi-modality research into understanding the combined effect patho-physiology, hematology and imaging features.

- Good article which can be used as a platform for future implications in imaging, pathobiologic and therapeutic studies.

THANK YOU FOR YOUR ATTENTION