The Daily COVID-19 Literature Surveillance Summary

November 20, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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EXECUTIVE SUMMARY

Epidemiology

- A retrospective case series conducted by radiologists from Zucker School of Medicine at Hofstra/Northwell in Manhasset, NY evaluated imaging features of six patients (all >65 years old) who presented to the emergency department with PCR-confirmed moderate-to-severe SARS-CoV-2 infection that was complicated by thromboembolic events. These authors suggest a hyper-inflammatory state secondary to SARS-CoV-2 infection may increase susceptibility to systemic thrombosis and recommend venous thromboembolism (VTE) prophylaxis in severe COVID-19 cases.

Understanding the Pathology

- Australian pulmonologists respond to recently published data by Mo et al, 2020 that showed diffusion capacity of carbon monoxide (DLCO) and carbon monoxide transfer coefficient (KCO) in COVID-19 patients reduced by 50% and 25% after recovery, respectively. They caution against interpreting these findings as attributable only to reduced alveolar volume and instead propose that lung fibrosis in COVID-19 associated acute respiratory distress syndrome (ARDS) may lead to loss of alveolar units and disrupt the alveolar-capillary barrier. Since pulmonary vascular abnormalities (i.e. vascular pruning, reduced blood flow) may alter DLCO, authors recommend further studies using more specific measures (i.e. combined DLCO and DLNO measurements or advanced imaging techniques) to clarify the pathophysiology underlying reduced gas exchange.

Management

- Emergency Medicine and Critical Care physicians in Saudi Arabia conducted a prospective observational analysis using a point-of-care ultrasound (POCUS) with the Riyadh Residual Lung Injury in COVID-19 (RELIC) scale to predict the evolution of lung injury in 171 severe COVID-19 patients and found that the combination of the two modalities were able to predict evolving interstitial lung disease with a sensitivity of 0.82 (95% CI: 0.76–0.89) and specificity of 0.91 (95% CI: 0.94–0.95).

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EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

THROMBOEMBOLIC COMPLICATIONS OF COVID-19

Mui LW, Lau JF, Lee HK.. Emerg Radiol. 2020 Nov 7. doi: 10.1007/s10140-020-01868-0. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A retrospective case series conducted by radiologists from Zucker School of Medicine at Hofstra/Northwell in Manhasset, NY evaluated imaging features of six patients (all >65 years old) who presented to the emergency department (ED) in April of 2020 with moderate-to-severe SARS-CoV-2 infection (confirmed via PCR) that was complicated by thromboembolic events (see summary). These authors suggest a hyper-inflammatory state secondary to SARS-CoV-2 infection may increase susceptibility to systemic thrombosis and recommend venous thromboembolism (VTE) prophylaxis in severe COVID-19 cases.

SUMMARY

Summary of each case below:
1. An otherwise healthy 46 year old male presented to the ED 6 days after a COVID-19 diagnosis with fever and hypoxia. Chest CT angiography showed extensive bilateral peripheral and lower lobe ground-glass opacities, bilateral interlobar pulmonary arterial emboli extending to bilateral upper and lower lobe segmental and subsegmental pulmonary arteries, and aortic arch thrombosis (Figure 1). His course was later complicated by respiratory failure and sepsis, and he died on hospital day 10.
2. A 40 year old male with hypertension and type 2 diabetes was admitted with hypoxemic respiratory distress secondary to COVID-19 infection and presented to the ED 7 days after discharge with agitation, acute encephalopathy, aphasia, and apraxia. Head CT revealed multiple infarcts in left frontal, bitemporal, and parietal lobes with petechial hemorrhagic foci in the right parietal lobe. Head CTA revealed multiple sites of thrombi distributed in various arterial sites (common carotid arteries, right internal carotid artery, bilateral external carotid arteries, and multiple bilateral M3 segmental occlusions) consistent with thromboembolic stroke (Figure 2). His admission course was complicated by worsening intracranial hemorrhage, and he had residual difficulties with speech, verbal comprehension, self-feeding, and continence upon 4 month follow-up.
3. A 62 year old male with hypertension, hyperlipidemia, and HIV presented with worsening shortness of breath, cough, fever, and poor appetite for 1 week and was found to be COVID-19 positive via PCR and hypoxemic (77% oxygen saturation). Chest CTA revealed extensive ground-glass and patchy airspace opacities, bilateral lower lobe segmental pulmonary emboli, and right ventricular thrombus. Echocardiogram also showed right ventricular thrombus with high probability of concomitant pulmonary embolism. The patient was given tPA and parenteral heparin, and ultimately discharged on day 15.
4. A 54 year old male with hyperlipidemia presented to the ED with right flank pain, fever, and cough. He was started on oral antibiotics for presumed pneumonia 3 days prior. COVID-19 testing in the ED was positive, and chest CT showed right lower lobe pulmonary embolism with thrombus and associated focal infarction in posterior tributaries in the right renal vein (Figure 4). Anticoagulation was initiated (heparin, then enoxaparin), and the patient was discharged home 3 days later on apixaban.
5. A 50 year old male with hypertension and hyperlipidemia was admitted with 2 weeks of progressive dyspnea, fever, cough, nausea, and diarrhea, followed by diagnosis of COVID-19 and discharge home. He was subsequently readmitted due to worsening hypoxemic respiratory distress. On hospital day 10 he developed sudden-onset left upper and lower extremity weakness, left facial paralysis, and decreased responsiveness. CT head showed acute right parietal infarct and focal distal ascending aortic thrombus. tPA was initiated, but complications ensued including hemodynamic instability, rapid atrial fibrillation, acute left lower extremity thrombosis, followed by cardiopulmonary arrest and death 2 days later.
6. A 61 year old male with hypertension, type 2 diabetes mellitus and hyperlipidemia was admitted due to 5 days of fever, cough, and dyspnea that were consistent with COVID-19 pneumonia, eventually requiring mechanical ventilation for progressive hypoxemic respiratory failure. Further complications included ST-elevated myocardial infarction and GI bleed, with subsequent CTA showing aortic and celiac artery thrombi. The patient died 2 weeks after admission.

ABSTRACT

The symptomology of patients afflicted with novel 2019 coronavirus disease (SARS-CoV-2 or COVID-19) has varied greatly, ranging from the asymptomatic state to debilitating hypoxemic respiratory failure caused by severe atypical viral pneumonia. Patients may also develop a hyper-inflammatory state that can lead to multi-organ failure. It has become increasingly apparent that, as part of the hyper-inflammatory state, COVID-19 infection increases susceptibility to systemic thromboembolic complications that can contribute to rapid clinical deterioration or demise. This article aims to review imaging features of various systemic thrombotic complications in six patients with moderate to severe disease. This case series includes examples of pulmonary embolism, stroke, right ventricular thrombosis, renal vein thrombosis, and aortic thrombosis with leg ischemia.

FIGURES

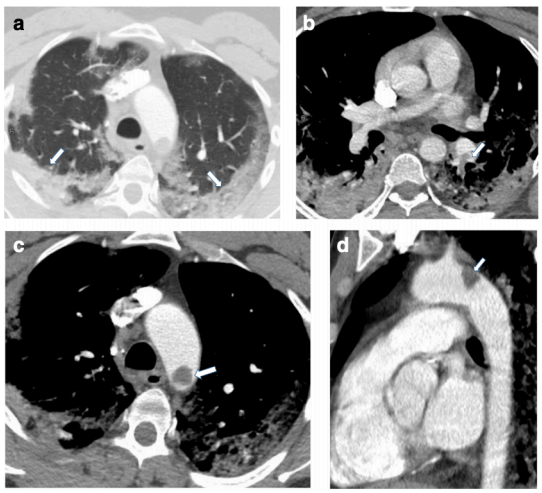


Figure 1. A 46-year-old man who presented with fever, cough, and shortness of breath. a Axial image shows bilateral peripheral ground-glass opacities (white arrows) commonly seen in COVID19 pneumonia. b Axial image shows numerous bilateral pulmonary emboli, including left lower lobe segmental pulmonary embolism. c and d Axial and sagittal images show focal partially adherent aortic arch thrombus (white arrow)

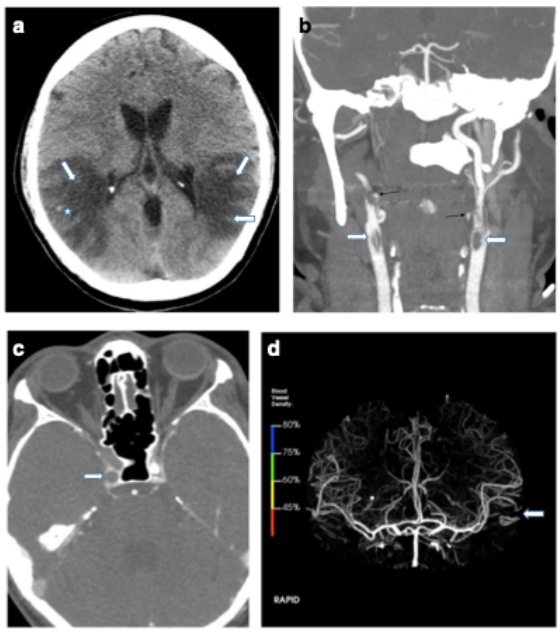


Figure 2. A 40-year-old man with hypertension and type 2 diabetes mellitus who presented with agitation, violent outburst, and aphasia and underwent head and neck CTA. a Axial non-contrast head CT image shows bilateral temporal infarcts (white arrows) with areas of petechial hemorrhage (star) as well as infarcts in the left frontal and parietal lobes (not shown). b Coronal maximal intensity projection (MIP) image demonstrates thrombi in bilateral distal common carotid arteries extending to carotid bulbs (white arrows), right internal carotid artery, and bilateral external carotid arteries (thin arrows). c Axial CTA image shows occlusion of the right internal carotid artery (white arrow). d RAPID image reveals an abrupt reduction in blood flow in the left M3 segment (white arrow)

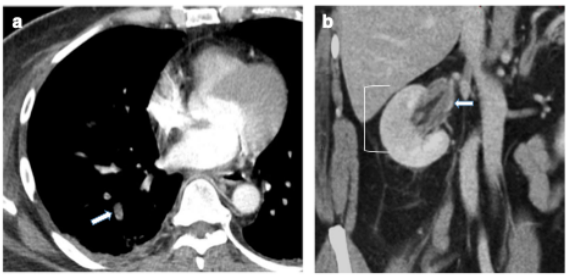


Figure 4. A 54-year-old man with3 days of right flank pain and negative urinalysis who underwent abdominal CT. a Axial CT image demonstrates right lower lobe segmental pulmonary embolus (white arrow). b Coronal CT im- age shows thrombosed posterior tributaries of the right renal vein (white arrow) and renal infarction (white left bracket)

UNDERSTANDING THE PATHOLOGY

CAUTION IN INTERPRETATION OF ABNORMAL CARBON MONOXIDE DIFFUSION CAPACITY IN COVID-19 PATIENTS

Chapman DG, Badal T, King GG, Thamrin C.. Eur Respir J. 2020 Nov 5:2003263. doi: 10.1183/13993003.03263-2020. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Australian pulmonologists respond to recently published data by Mo et al, 2020 that showed diffusion capacity of carbon monoxide (DLCO) and carbon monoxide transfer coefficient (KCO) in COVID-19 patients reduced by 50% and 25% after recovery, respectively. They caution against interpreting these findings as attributable only to reduced alveolar volume and instead propose that lung fibrosis in COVID-19 associated acute respiratory distress syndrome (ARDS) may lead to loss of alveolar units and disrupt the alveolar-capillary barrier (Figure 1). Since pulmonary vascular abnormalities (i.e. vascular pruning, reduced blood flow) may alter DLCO, authors recommend further studies using more specific measures (i.e. combined DLCO and DLNO measurements or advanced imaging techniques) to clarify the pathophysiology underlying reduced gas exchange.

FIGURES

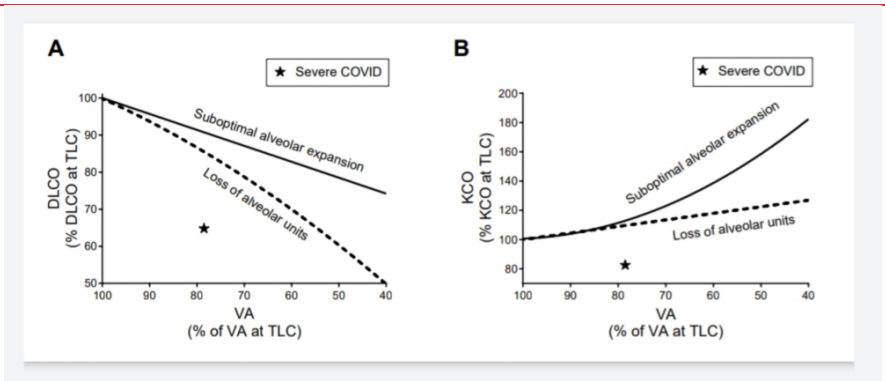


Figure 1. The relationship between alveolar volume (VA) and, [A] diffusing capacity for carbon monoxide (DLCO) and [B] rate constant for CO uptake (KCO), are plotted as a percentage of the value at total lung capacity (TLC). The relationships are shown for two situations that result in reduced VA; i) suboptimal alveolar expansion (DLCO and KCO measured at volumes below maximum TLC, solid line), ii) loss of alveolar units (e.g. theoretical removal of lobules or lobes with remaining lung expanded to its normal TLC, dashed line). The star ( ) represents the group mean data of the 'severe pneumonia' from Mo et al (1). Mean VA was calculated as mean percent predicted DLCO/ mean percent predicted KCO. The relationship between VA, DLCO and KCO was calculated using the equations as described in (3) : for suboptimal alveolar expansion, KCO= 0.43 + (0.57/VA); for loss of alveolar lung units, change in KCO = 0.4x + 2.1 where x = the proportion of volume diverted to the remaining lung; for both scenarios, DLCO = VA*KCO.

CRITICAL CARE

RESIDUAL LUNG INJURY IN PATIENTS RECOVERING FROM COVID-19 CRITICAL ILLNESS: A PROSPECTIVE LONGITUDINAL POINT-OF-CARE LUNG ULTRASOUND STUDY

Alharthy A, Abuhamdah M, Balhamar A, Faqihi F, Nasim N, Ahmad S, Noor A, Tamim H, Alqahtani SA, Abdulaziz Al Saud AAASB, Kutsogiannis DJ, Brindley PG, Memish ZA, Karakitsos D, Blaivas M.. J Ultrasound Med. 2020 Nov 13. doi: 10.1002/jum.15563. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

Emergency Medicine and Critical Care physicians conducted a prospective observational analysis using a point-of-care ultrasound (POCUS) with the Riyadh Residual Lung Injury in COVID-19 (RELIC) scale to predict the evolution of lung injury in severe COVID-19 (defined as having Acute Respiratory Failure: dyspnea, respiratory rate above 30, O2 Saturation below 93%, PaO2/FiO2 ratio less than 300, and/or development of bilateral pulmonary infiltrates within 24-48 hours) patients (n=171) in Riyadh, Saudi Arabia over four months (Table 5). Findings show that the combination of the two modalities were able to predict evolving interstitial lung disease with a sensitivity of 0.82 (95% CI: 0.76–0.89) and specificity of 0.91 (95% CI: 0.94–0.95) (Figure 4, Table 6). The authors recommend providers integrate lung ultrasound into clinical models (ie., POCUS + RELIC) to predict lung disease severity and outcomes after acute COVID-19.

ABSTRACT

Scarce data exist regarding the natural history of lung lesions detected on ultrasound in those who survive severe COVID-19 pneumonia. OBJECTIVE: We performed a prospective analysis of point-of-care ultrasound (POCUS) findings in critically ill COVID-19 patients during and after hospitalization. METHODS: We enrolled 171 COVID-19 intensive care unit patients. POCUS of the lungs was performed with phased array (2-4 MHz), convex (2-6 MHz) and linear (10-15 MHz) transducers, scanning 12 lung areas. Chest computed tomography angiography was performed to exclude suspected pulmonary embolism. Survivors were clinically and sonographically evaluated during a 4 month period for evidence of residual lung injury. Chest computed tomography angiography and echocardiography were used to exclude pulmonary hypertension (PH) and chest high-resolution-computed-tomography to exclude interstitial lung disease (ILD) in symptomatic survivors. RESULTS: Cox regression analysis showed that lymphocytopenia (hazard ratio [HR]: 0.88, 95% confidence intervals [CI]: 0.68-0.96, p = 0.048), increased lactate (HR: 1.17, 95% CI: 0.94-1.46, p = 0.049), and D-dimers (HR: 1.21, 95% CI: 1.03-1.44, p = 0.03) were mortality predictors. Non-survivors had increased incidence of pulmonary abnormalities (B-lines, pleural line irregularities, and consolidations) compared to survivors (p < 0.05). During follow-up, POCUS with clinical and laboratory parameters integrated in the semi-quantitative Riyadh-Residual-Lung-Injury scale had sensitivity of 0.82 (95% CI: 0.76-0.89) and specificity of 0.91 (95% CI: 0.94-0.95) in predicting ILD. The prevalence of PH and ILD (non-specific-interstitial-pneumonia) was 7% and 11.8%, respectively. CONCLUSION: POCUS showed ability to monitor the evolution of severe COVID-19 pneumonia after hospital discharge, supporting its integration in clinical predictive models of residual lung injury.

Table 6. COVID-19 symptomatic survivors as stratified by the Riyadh Residual Lung Injury in COVID-19 (RELIC) scale at 4 months post-hospital discharge

	COVID-19 survivors (n = 127)	
RELIC scale (1–14)	**Symptomatic patients*(total number = 62)**	**Patients who developed interstitial lung disease**(total number = 15)**
1–5 (low risk)	3	0
6–9 (medium risk)	26	5
10–14 (high risk)	33	10

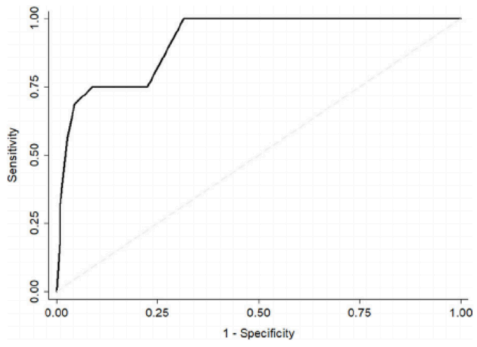
Abbreviations: RELIC scale = Riyadh Residual Lung Injury in COVID-19 scale.
*Patients with breathing difficulty and inability to complete a 6-min walking test.
**Interstitial lung disease confirmed by chest high-resolution computed tomography.
scan and lung biopsy (findings were consistent with non-specific interstitial pneumonia).

Table 5. Riyadh Residual Lung Injury in COVID-19 (RELIC) scale based on ultrasound and other parameters was tailored to predict residual lung injury post severe COVID-19 pneumonia

Parameters	**RELIC Scale (1–14)***
Symptoms prior to hospital admission	
Dyspnea	1 point
Fever	1 point
Laboratory parameters on hospital admission	
Lymphocyte count <0.8 x 10^9/L	1 point
Ferritin >336 ng/L and LDH > 250 U/L at presentation	1 point
D-dimers (> 1 mcg/mL)	1 point
Other parameters	
PaO_2 /FiO_2 ratio < 100 on admission	1 point
Mechanical ventilation >14 days during hospitalization	2 points
Ultrasound findings 2 to 4 months post-hospital discharge	
Pleural line irregularities >6 lung areas	2 points
Consolidations >3 lung areas	2 points
B-line like artifacts >3 lung areas	2 points

Abbreviations: RELIC scale = Riyadh Residual Lung Injury in COVID-19 scale; LDH = lactate dehydrogenase; PaO_2/FiO_2 ratio = partial arterial pressure of oxygen to fractional inspired concentration of oxygen ratio.*Patients with a score > 9 had a high risk in developing interstitial lung disease.

Figure 4. Receiver operator curve analysis for the Riyadh Residual Lung Injury in COVID-19 (RELIC) scale. A score > 9 had a sensitivity of 0.82 (95% CI: 0.76–0.89) and a specificity of 0.91 (95% CI: 0.94–0.95) in predicting the development of interstitial lung disease (Area-under-the curve 0.90 [95% CI: 0.84–0.95]; p = 0.001) 4 months post-hospital discharge.



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