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RESEARCH ARTICLE

LUNG ULTRASOUND COMBINED WITH D-DIMER TESTING FOR EARLY DETECTION OF PULMONARY INTRAVASCULAR COAGULOPATHY IN COVID-19 PNEUMONIA

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ABSTRACT

The outbreak of the coronavirus disease 2019 (COVID-19) has show a global spreading trend. Early and effective predictors of clinical outcomes are urgently needed to improve management of Covid-19 patients. Lung ultrasound (LUS) combined with D-Dimer (DD) testing could be a new strategy for early diagnosis in patients with suspected COVID-19 pneumonia associated with acute respiratory distress syndrome (ARDS) and helpful prevent the progression of intravascular pulmonary coagulopathy. Modern assay for D-dimer are monoclonal antibody based. The enzyme-linked immunosorbent assay (ELISA) is the reference method for D-dimer analysis. Elevated D-dimer levels are associated with clotting activation and fibrinolysis and can be used as indirect biomarkers of thrombosis than in combination with B-lines detected by lung ultrasound become highly sensitive in the diagnosis of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Careful attention needs to be paid to the initial diagnosis, prevention and treatment of the prothrombotic and thrombotic state that can occur in a substantial percentage of COVID-19 patients. We believe that lung ultrasound early detection in COVID-19 and a rapid D-dimer assay may provide better prognosis in these patients.

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the novel coronavirus first detected in Whan, Hubei, China, that cause coronavirus disease 2019 (COVID-19) (Lai *et al*., 2020; Lu H, 2020). This new coronavirus SARS-CoV-2 has a specific tropism for the lower respiratory tract, but causes severe pneumonia in a low percentage of patients. However, the rapid spread of the infection during this pandemic has caused the need to hospitalize a large number of patients. In comparison to pneumonia caused by influenza virus, the COVID-19 virus is characterised by rapid transmission with a high infection and high lethality rate. In addition to pneumonia affecting the small air sacs within the lungs, we are also finding hundreds of small blood clots throughout the lungs. This scenario is not seen with other types of lung infection and explains why blood oxygen levels fall dramatically in severe COVID-19 infection.

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Fogarty and collegues found that severe coronavirus disease 2019 (COVID-2019) infection is correlated with a significant coagulopathy that correlates with disease severity (Fogarty *et al*., 2020). The initial coaugulopathy of COVID-19 presents with prominent elevation of D-dimer and fibrin/fibrinogen degradation products, while abnormalities in prothrombin time,partial thromboplastin time, and platelet counts are relatively uncommon in initial presentations. Increased concentrations of circulating D-dimer (reflecting vascular lung thrombosis of the bed with fibrinolysis) is one key early features of severe pulmonary intravascular coagulopathy related to COVID-19. Patients with confirmed COVID-19 pneumonia have typical imaging features that can be helpful in early screening of highly suspected cases and in evaluation of the severity and extent of disease. The diagnostic value of lung ultrasound (LUS) and D-dimer (DD) as a new molecular marker for thrombus formation in initial COVID-19 coagulopathy they could be a useful novel strategy in critically ill patients with respiratory symptoms of unexsplained origins who underwent a chest X-ray (CXR) in emergency departments (ED).

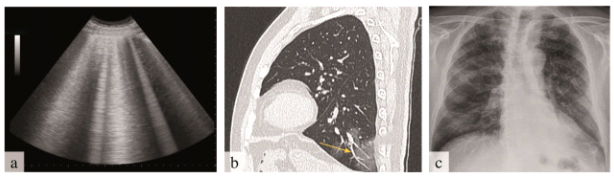

Figure 1. Chest Diagnostic Imaging Findings of Coronavirus Disease 2019 (Covid-19) Pneumonia

Lung Ultrasound (LUS) of interstitial syndrome, characterized by the presence of three or more B-lines between two ribs. B-lines are hyperechoic laser-like artifacts that resemble a comet tail, arise from the pleural line. (b)High-Resolution Computed Tomography (HRCT) sagittal image shows ground-glass opacities (GGO) in the posterior and inferior segment of left lower lobe with vascular enlargement (yellow arrow). (c) Chest X-ray (CXR) image shows bilateral pulmonary groud-glass opacities

Elevated D-dimer levels are associated with clotting activation and fibrinolysis and can be used as indirect biomarkers of thrombosis than in combination with B-lines detected by lung ultrasound (LUS) become highly sensitive in the diagnosis of pulmonar intravascular coagulopathy in COVID-19 pneumonia. The characteristic visible in all patients with pneumonia is ground-glass opacities (GGO), a descriptive term indicating an interstitial alteration of the lung parenchyma, associated with multi-lobar and posterior involvement, bilateral distribution, and subsegmental vessel enlargement. Vessel enlargement was described in the vicinity of areas with GGO, which is compatible with thromboinflammatory processes. Subsegmental vascular enlargement in areas of lung opacity was observed in (89%) of patients with confirmed COVID-19 pneumonia.

Although in situ thrombosis in certainly a possibility, these finding could be due to hyperemia and increased blood flow.
Most patients with COVID-19 pneumonia have GGO or mixed GGO and consolidation and vascular enlargement in the lesion. Lesions are more likely to have peripheral distribution and bilateral involvement and be lower lung predominant and multifocal. CT involvement score can help in evaluation of the severity and extent of the disease. High-resolution computed tomography (HRCT) scans remain the gold standard imaging technique for thoracic evaluation, but transporting patients outside the intensive care unit (ICU) is difficult and potentially harmful. Bedside chest X-ray (CXR) is still considered the standard of care for many diagnostic applications in the ICU. However, this imaging technique has important methodological limitations and often produces low accuracy.

As lung abnormalities may develop before clinical manifestations and nucleic acid detection, experts have recommended early chest CT for screening suspected patients. Unfortunately CT can't be used routinely because of high cost, radiation exposure and scarce availability in low resources setting. Thus, in clinical practice, chest radiography represents the standard of care and is mostly used to diagnose pneumonia. However, in patients evaluated in the emergency department (ED), CXR showed a poor sensitivity (43.5%) when compared to CT (Self, 2013). Therefore, reliance on CXR to diagnose pneumonia may lead to significant rates of misdiagnosis. Lung ultrasound (LUS) is an emerging bedside diagnostic tool with a sensitivity of (94%) and a specificity of (96%) for the diagnosis of pneumonia according to a recent metanalysis (Chavez, 2014).
A life threatening complication of SARS-Co-V-2 infection is an acute respiratory distress syndrome (ARDS), wich occurs more often in older adults, those with immune disorders and co-morbidities. Recent observations suggest that respiratory failure in COVID-19 is not driven by the development of the acute respiratory distress syndrome (ARDS) alone, but that (microvascular) thrombotic processes may play a role as well.
This may have important consequences for the diagnostic and therapeutic management of these patients. There is a strong association between D-dimer levels, disease progression and chest CT features suggesting venous thrombosis. D-dimer is a degradation product of cross-linked fibrin and reflects blood clot formation and its subsequent fibrinolysis. Testing uses an enzyme-linked immunoabsorbent assay (ELISA) such as VIDAS D-Dimer test, with generates results within 1 hour and has sensitivity of (94%) to (100%); specificity of (38%); negative predictive value (NPV) of greater than 99; positive predictive value (PPV) of (60.8%), at a cut-off 500 ng/mL (Mountain, 2007). Acute COVID-19 pneumonia has features of a distinctive acute interstitial pneumonia with a diffuse alveolar damage component, coupled with microvascular involvement with intra- and extravascular fibrin deposition and intravascular trapping of neutrophilis, and frequently, with formation of microthrombi in arterioles.

Lung ultrasound (LUS) provides results similar to HRCT and superior to standard chest CXR for the assessment of pneumonia and/or ARDS with the added benefit of ease of use at the point-of-care (POC) (Figure 1). B-lines are early finding of COVID-19, even in mild symptomatic subjects. In the most serious cases such as pre-ARDS or ARDS the B-lines end up filling the ultrasound image almost completely, until it merges, so as to create a single hyperechoic image named as "white lung", with distortion and irregularity of the pleural line. This represents a key part of monitoring critical patients in ICU as it allows the intensivist to examine the lung and pleural space.

In advanced stage, lung consolidations are present, representing pulmonary pathological areas that are no longer normally ventilated. D-dimer was dichotomized as either less than or greater than 0.5 μg/liter, with more patients with severe disease experiencing a primary outcome having D-dimer values >0.5 μg/liter (Metlay, 2019). D-dimer on admission greater than 2.0 μg/mL could effectively predict in hospital mortality in patients with COVID-19, which indicates D-dimer could be an early and helpful marker to improve management of COVID-19 patients (Zhang, 2020). Various studies in patients with COVID-19 have consistently shown a very strong association between increased D-dimer levels and severe disease/poor prognosis. A combination of lung ultrasound and D-dimer testing (LUS-DD) could be an optimal new strategy for early diagnosis in patients with suspected COVID-19 pneumonia and helpful prevent the progression of intravascular pulmonary coagulopathy and would constitute a potential advantage in terms of survival and implement pioneering therapies for the treatment of inflammatory and hyperinflammatory states in patients who may develop acute lung damage that may progress to respiratory failure, although multi-organ failure may occur.

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Author's Contributions

This work was carried out in collaboration among the authors. Author TE prepared and wrote the manuscript, conceived imaging and developed concept and ideas. Authors SV and LR helped within the clinic. Author GT contributed the supervised the manuscript.

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