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Exploring Histomorphological Changes in Lungs Induced by Severe COVID-19: A Comparative study using CT Scan and Lung Ultrasound Assessment

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A B S T R A C T

Background: Individuals with COVID-19 may experience respiratory collapse due to severe bilateral pneumonia. Because there was a substantial threat of infections during biopsies, histological samples are rare.

Objective: The present study aimed to assess the histomorphological alterations in the lungs affected by COVID-19 using a CT scan and lung ultrasonography.

Methodology: We conducted a prospective observational study on individuals who had severe COVID-19. Twelve exploration zones were created from the thorax to link lung ultrasonography (LU) and CT-scan findings. Each block was split into 7 cuts of 2.5µm thick sections. Specimens for Histology were stained with Weigert-Van-Giesson (to evaluate elastic fiber architecture) and Masson's trichrome eosine and hematoxylin, (for collagen deposition and fibrosis). SPSS 20 was used for the analysis of the data.

Results: The patients' mean age was 61.65 ± 12.57 years, with 96% of them being male. A total of 179 thoracic areas were examined in 25 individuals who underwent evaluation using both thoracic LU and chest CT scans. B2-lines were the most common LU finding (49.7%). Ground-glass opacity (GGO), was the most common CT-scan result (31.3%). Findings from a pathological CT scan were frequently seen when B2-lines or C-lines were found using LU (positive predictive value, PPV, 85.1%). Diffuse alveolar damage (DAD) accounted for 75% of the histological samples, while persistent interstitial inflammation (25%).

Conclusion: Lung Ultrasonography (LU) frequently reveals B2-lines and C-profiles in patients experiencing severe COVID-19 and respiratory impairment. These findings often correspond to various CT patterns and histological outcomes such as Diffuse Alveolar Damage (DAD) and lung fibrosis. LU holds potential in predicting prognosis, assessing response to therapy, and optimizing the necessity for CT scans.

Keywords: Histomorphological Changes; Lungs; Ultrasound Assessment; Ground-glass opacity; Diffuse alveolar damage

Introduction

Coronavirus disease (COVID-19) is an infection caused by the new coronavirus SARS-CoV-2, which causes severe acute respiratory illness. Interstitial pneumonia, which affects COVID-19 patients, can result in acute respiratory distress syndrome (ARDS) (31%) and respiratory failure (54%), among other complications.[1] The COVID-19 virus is widely distributed worldwide.[2] As scientific data grows, strategies for monitoring and therapy are being improved. A useful tool for diagnosis, clinical care, and therapeutic guidance is chest imaging. To diagnose pneumonia, chest radiography is first carried out, and computed tomography (CT) is advised to assess ARDS and other possible consequences more thoroughly.[3] Bilateral peripheral consolidations and ground-glass opacity (GGO) are the principal radiological findings.[4-6] Additional symptoms, for traction bronchiectasis and pneumonia, may appear when ARDS progresses.[7-9] While CT scans of the chest provide expedient evidence for treatment planning, several obstacles were observed during the COVID-19 outbreak. These include the possibility of infection for medical personnel, the requirement for cleaning and disinfection of surfaces and spaces, the potential for fatality for critically ill patients during transfer, and the inconvenience of tracking the course of the disease or compromised respiratory conditions will be challenging in mobilization.[3] As a crucial monitoring technique for COVID-19 patients in both intensive care units (ICUs) and intermediate respiratory care units (IMCUs), lung ultrasonography (LU) has been developed.[10,11] LU is simple to use, reproducible, and repeatable. It enables quick bedside use, which promotes quick decision-making.[12]

When white lung, subpleural consolidations, or convalescents B-lines, are present, an alveolar–interstitial pattern may be recognized and tracked by LU.[13-15] There have been some preliminary reports of connections between LU and CT patterns.[3] The pathological results behind this radiological imaging of lung injury caused by COVID-19 are yet unknown, nevertheless. A better targeting of therapy choices would need a knowledge of the disease's histopathology. On the other hand, a biopsy of the lungs in cases of severe infection caused by COVID-19 may be linked to both clinical worsening and perhaps fatal consequences. DAD with fibromyxoid interstitial deposition and cellular interstitial pattern together with microthrombi in tiny arteries, are the most common histopathological findings of biopsies.[16-19] Different damage histomorphological patterns may correlate with certain tomographic and/or ultrasound patterns. Determining the characteristics of the lung pictures that correlate with various histology findings may aid in therapy optimization and prognostication. Our goal was to link CT-scan characteristics and LU results with histology COVID-19 traits. According to the literature, numerous studies have been carried out on the association of pneumonia bilateral subpleural consolidations, pleural thickening, and multifocal B lines,[12] which reveal abnormalities noticeable on CT scans of chest.[14] It is yet unknown, nevertheless, how LUS and CT findings compare in individuals who are critically ill and admitted to the hospital due to severe COVID-19 pneumonia.

Objective

The present study aimed to assess the histomorphological alterations in the lungs affected by COVID-19 using a CT scan and lung ultrasonography.

Methodology

This observational prospective study included 25 consecutive patients with severe COVID-19 with progressive worsening despite supportive care who were evaluated through CT scan and LU. The study was carried out at Ayub Medical College, Abbottabad, and Women Medical College, Abbottabad from January 2021 to December 2022. The total sample size in our study was 25 patients which were selected according to a previous study done by Trias-Sabrià P et al,[9] based on this study sample size for our study was 28 but unfortunately due to some factors we missed 3 patients so the final sample size was 25.

All procedures used in this study involving human subjects complied with ethical guidelines. The PCR verified the COVID-19 diagnosis, and the informed agreement of the family for a transthoracic biopsy met the inclusion requirements. A clinical deterioration brought on by extrapulmonary problems or by causes other than COVID-19 lung damage was among the exclusion criteria. Data on the patient's history of illnesses, the length of time it has been since the appearance of symptoms started, the results of blood tests, clinical, radiographic, and laboratory tests, as well as the course of therapy, were gathered. The LU results were presented by the global evidence-based guidelines.[13]

An experienced pulmonologist with team of anatomist conducted a focused LU examination. The Lumify application and a portable Samsung tablet were attached to a Philips Lumify C5-2 transducer. The convex transducer was configured in lung configuration for the LU evaluation. To minimize contamination and enhance sterilization, the sampling tools were covered in sterilized disposable plastic bags. When evaluating lung function in highly contagious illnesses like COVID-19, wireless transducers could be useful.[20,21] Following current guidelines, the transducer and wireless tablet (Instrument used for assessment) were sterilized at the end of the investigation.[22] As previously mentioned in the previous

Table 1. Individual's demographics and clinical features at the time of assessment based on lung ultrasonography score

	Total No. of individuals (n=25)	worsening (n=10)
Individual's History		
Smokers	8 (32%)	4 (40%)
Hypertension	17 (68%)	7 (70%)
Dyslipidemia	12(48%)	4 (40%)
Diabetes	7 (28%)	3 (30%)
Obesity	8 (32%)	3 (30%)
COPD	3 (12%)	1 (10%)
Asthma	2 (8%)	1 (10%)
Cardiopathy	2 (8%)	1 (10%)
Hepatopathy	1 (4%)	1 (10%)
Malignancies	7 (28%)	5 (50%)
Chronic Kidney Disease	3 (12%)	1 (10%)
Blood Test		
LDH (U/L)	415	435
CRP (mg/L)	71.55	165.77
Ferritin (μg/L)	990.80	1341.55
Leukocyte count (×109/L)	13.11	15.6
Lymphocyte count (×109/L)	0.94	0.74

investigations,[11,13] the ultrasonography results were evaluated using the LU score (LUS). In summary, LUS assesses lung parenchyma after a thoracic zone assessment.[23,24]

The sections of the chest wall that are posterior (paravertebral line), lateral (midaxillary line), and anterior (midclavicular line) were split into inferior and superior halves. Subjects who could sit or tilt sideways were asked to explore their posteriors. If posterior access was not feasible, posterior axillary line exploration was used in its place. In order to facilitate pleural and lung examination, the transducer was positioned vertically against ribs. Then, each region was scored in accordance with the guidelines for point of care lung ultrasound [13,14] subpleural consolidation scored 3. The LUS, which ranged from 0 to 36 points, was determined by the total of the scores[13,14]

When a patient's condition started to worsen, LU and CT scans were performed on all 25 patients. Their descriptions of lung parenchyma in each of the 12 areas used in LUS were provided by two skilled thoracic radiologists. The histology data and LUS were hidden from both radiologists. Each CT scan was examined separately before being agreed upon. In 37% of cases, endovenous-contrast was employed. 179 exploration areas in all were evaluated. Identifications included GGO, consolidation, organized pneumonia, thickening of the septa, and fibrosis. The LU results and radiological findings matched.

Biopsies were preserved in 4% formaldehyde for 24 hours before being paraffin-embedded. Each block was split into 7 cuts of 2.5μm thick sections. Specimens for

Table 2. Thoracic regions observed by CT-Scan and LU.

LU	CT-SCAN						Total regions %
	Normal	GGO	C	CP	PT	PE	
A-Lines N (%)	6 (40%)	6 (40%)	1 (6.66%)	2 (13.2%)	0	0	15(8.3%)
B1-Lines N (%)	7 (22.5%)	10 (24.8%)	6 (19.3%)	6 (19.3%)	1 (3.22%)	1 (3.22%)	31 (17.3%)
B2-Lines N (%)	10 (11.2%)	27 (30.2%)	21 (23.5%)	29 (32.4%)	0	2 (2.24%)	89 (49.7%)
C-Profile N (%)	5 (11%)	13 (28.6%)	19 (41.8%)	4 (8.8%)	0	2 (2.24%)	44 (24.5%)
Total regions N (%)	28 (15.6%)	56 (31.3%)	47 (26.2%)	41 (22.9%)	1 (0.56%)	5 (2.79%)	179(100%)
LU=Lung ultrasound, PE=Pleural effusion, PT=Pneumothorax, CP=crazy paving, C=consolidation, GGO=ground glass opacity,							

Histology were stained with Weigert-Van-Giesson (to evaluate elastic fiber architecture) and Masson's trichrome eosine and hematoxylin, (for collagen deposition and fibrosis). The histological sample's slides were observed on a Histech scanner at a resolution of 40X to acquire entire slide pictures. Two skilled pulmonary pathologists made the histological diagnosis (while remaining blind to clinical and radiological data).

Frequency and percentages were used to characterize categorical data. When a variable was regularly distributed, continuous variables were reported as standard deviation and mean; otherwise, they were written as interquartile range and median. The predictive values, negative and positive (NPV and PPV), were computed. R (Software Version 3.6.0) and SPSS 20 was used for the analysis of the data.

Results

The research comprised twenty-five individuals who showed signs of deteriorating illness. There was a median interval of 6 days between the CT scan and LU, and 7 days between the CT scan and histology. Histology samples were obtained under LU guidance. There were 24 patients (96%) who were male, and the mean age was 61.65 ± 12.57 years. Patients had full COVID-19 therapy in accordance with the authorized protocol. The comorbidities that were most common were dyslipidemia (48%), hypertension (68%), and a history of cancer (28%). Table 1 describes the clinical and demographic features of the patients who were included.

A total of 179 thoracic areas were examined in 25 individuals using comparative lung ultrasonography and CT scanning. B2-lines (89/179 thoracic regions; 49.7%) were the most common LU finding, followed by A-lines (15/179; 8.3%), C-profile (44/179; 24.5%), and B1-lines (31/179; 17.3%). With an average LUS of 22.5 ± 5.9 points, the pattern of alveolar–interstitial disease is moderate–severe. The most common CT-scan finding was crazy paving (41/179; 22.9%), consolidation (47/179; 26.2%), and GGO (56/179 thoracic regions; 31.3%). Results from CT scan and LU are displayed in Table 2.

From 13 patients, 25 echo-guided histology samples were taken. The identical LU results were seen in both hemithoraxes by all individuals. The lung parenchyma was not represented in the samples taken from a single patient. Of the 24 samples that were left, 17 (71%) had DAD and 5 (21%) had interstitial inflammation of chronic nature. The damage patterns detected in the studied DAD were varied, exhibiting several progressive stages, such as exudative 7/21, 31.1%), and fibrotic (9/25, 32.5%). Two lesions were identified in individuals with either an acute or exudative pattern: a typical hyaline membrane and a fibrin "plug" in the alveolar space (acute fibrinous organizing pneumonia). Collagen fibrosis was the most common fibrotic finding and was often linked to pneumocyte hyperplasia. Just two samples (8.3%) had consistent fibrosis with architectural alteration. There were no signs of microthrombi or microangiopathy.

In the 12 individuals, lung ultrasonography results were correlated with histological findings using typical lung biopsy samples. Only the C-profile and B2-lines were found in these instances. A C-profile was reported in 4 (33.3%) of the patients. Histological evidence of lung fibrosis and DAD was seen in these instances. Collagen deposition was the main finding in two (50%) of them, and AFOP in the other two. 16 locations (66.7%) had B2-lines found; the most common finding in 6 of these regions (37.5%) was the presence of hyaline membrane, followed by fibrosis in six samples (37.5%) and organized pneumonia in two samples (12.5%). In these individuals, there were no B1-lines or A-lines.

Discussion

The current findings demonstrate that C-lines and B2-lines, which are histologically linked with various symptoms of DAD, such as AFOP regions and hyaline membranes, as well as lung fibrosis, are present in several individuals infected with SARS CoV-2 virus who have progressive respiratory failure. Since both were present in all LU patterns, there was no particular LU imaging link between crazy-paving regions and GGOs in the CT scan. However, LU B2-lines and C-lines had a higher prevalence of CT regions of consolidation.

In individuals having COVID-19, B-lines predominate and can show as a brilliant white lung in both distinct (B1) and coalescent (B2) forms. Bilateral patchy clusters also exhibit subpleural consolidations (C-profile) and irregular pleural lines, which are primarily observed in the inferior and posterior regions.[24,26–28] In our study, a total of 179 thoracic areas were examined in 25 individuals using comparative lung ultrasonography and CT scanning. B2-lines (89/179 thoracic regions; 49.7%) were the most common LU finding, followed by A-lines (15/179; 8.3%), C-profile (44/179; 24.5%), and B1-lines (31/179; 17.3%). With an average LUS of 22.5 ± 5.9 points, the pattern of alveolar–interstitial disease is moderate–severe. The most common CT-scan finding was crazy paving (41/179; 22.9%), consolidation (47/179; 26.2%), and GGO (56/179 thoracic regions; 31.3%). These findings are from the previous study, which reported almost similar results.[9] These results might be used to forecast the clinical results for patients referred to the intensive care unit.[28] Additionally, the current data support earlier research showing that a greater LUS not only corresponds with more abnormal CT findings but also suggests a worse clinical outcome.7 Consequently, LUS might support the rationale for a CT scan as well as aid in the monitoring of the patient's clinical development at the bedside.

In hospitalized COVID-19 patients, a study[29] conducted a two-centered retrospective comparison of CT-scan imaging and LU. Lungs ultrasound discovered 63% of the positive locations overall. On the other hand, 38.7% of the locations on the CT scan were abnormal. The results of the LU and CT scans indicated that COVID-19 lesions had a higher propensity to develop bilaterally in the posterior lung areas. Because we only included individuals with severe COVID-19, our research has greater radiological abnormalities. From 13 patients, 25 echo-guided histology samples were taken. The identical LU results were seen in both hemithoraxes by all individuals. The lung parenchyma was not represented in the samples taken from a single patient. Of the 24 samples that were left, 17 (71%) had DAD and 5 (21%) had interstitial inflammation of chronic nature. The damage patterns detected in the studied DAD were varied, exhibiting several progressive stages, such as exudative 7/21, 31.1%), and fibrotic (9/25, 32.5%). Two lesions were identified in individuals with either an acute or exudative pattern: a typical hyaline membrane and a fibrin "plug" in the alveolar space (acute fibrinous organizing pneumonia). Collagen fibrosis was the most common fibrotic finding and was often linked to pneumocyte hyperplasia. Just two samples (8.3%) had consistent fibrosis with architectural alteration. There were no signs of microthrombi or microangiopathy.

These results are in line with previously published data: the primary histopathological evidence was DAD, which included several histopathological abnormalities such as persistent interstitial lung disease and AFOP regions alongside collagen fibrotic areas.[9,26,29]

In the 12 individuals, lung ultrasonography results were correlated with histological findings using typical lung biopsy samples. Only the C-profile and B2-lines were found in these instances. A C-profile was reported in 4 (33.3%) of the patients. Histological evidence of lung fibrosis and DAD was seen in these instances. Collagen deposition was the main finding in two (50%) of them, and AFOP in the other two. 16 locations (66.7%) had B2-lines found; the most common finding in 6 of these regions (37.5%) was the presence of hyaline membrane, followed by fibrosis in six samples (37.5%) and organized pneumonia in two samples (12.5%). In these individuals, there were no B1-lines or A-lines. These results are consistent with the previous study done by Trias-Sabrià P et al.[9]

The primary constraint on our research is the smaller sample size resulting from challenges in obtaining both lung ultrasounds and CT scans at the appropriate timeframe of respiratory deterioration in COVID-19-infected individuals.

Conclusions

Lung Ultrasonography (LU) frequently reveals B2-lines and C-profiles in patients experiencing severe COVID-19 and respiratory impairment. These findings often correspond to various CT patterns and histological outcomes such as Diffuse Alveolar Damage (DAD) and lung fibrosis. LU holds potential in predicting prognosis, assessing response to therapy, and optimizing the necessity for CT scans.

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