Prognostic Values of Lung Ultrasound Score in Hospitalized COVID-19 Pneumonia Patients

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Abstract:

COVID-19 is a respiratory virus acquired mainly by droplets and airborne particles from infected persons. High-resolution computerized tomography (HRCT) and polymerase chain reaction (PCR) are the standard diagnostic methods. Lung Ultrasound could be used as a complementary management tool.

Patients and methods: This was a cohort study conducted in the isolation unit of Assiut University Hospital from January 2022 to June 2023. As a specialized tertiary referral center, it received cases classified as severe or critical. The study included 82 confirmed COVID-19 pneumonia cases who underwent 3 rounds of chest ultrasound evaluation and were given a score according to ultrasound findings, with a score of 12 chosen as a cut-off point between high and low scores. The patients' clinical data and laboratory results were studied with every round.

Results: LUSS has shown good accuracy in classifying the severity of the disease, with 79.2% accuracy in predicting the severity of the infection and 79.4% accuracy in predicting mortality. It also proved its accuracy in predicting the prognosis of COVID-19 Pneumonia with an accuracy of 85.37%.

Conclusion: This study concluded that LUSS could be used successfully to predict the prognosis and outcome of COVID-19 pneumonia, which concurs with the results of previous studies.

Keywords: COVID-19, Pneumonia, Lung Ultrasound Score, Pandemic.

Introduction:

In 2019, the WHO declared the COVID-19 pandemic a pandemic (1). COVID-19 pneumonia has a variety of symptoms, including cough, fever, and shortness of breath. Symptoms range from mild to fatal (2).

The methods for diagnosis and follow-up of COVID-19 pneumonia are PCR of nasopharyngeal swab and High-Resolution Computerized Tomography (HRCT) of the chest and laboratory investigations, such as C-reactive protein, ferritin, lymphocytes, and lactate dehydrogenase (LDH) (3)(4). However, these methods are relatively expensive; thus, another method for diagnosis and follow-up was needed.

Lung Ultrasonography (LUS) has been routinely used in pulmonology to diagnose lung diseases like pneumonia with good sensitivity, specificity, and accuracy (5). LUS has been used successfully during the COVID-19 pandemic for early diagnosis, follow-up, and disease management (6). The typical findings in the LUS of the patients were pleural abnormalities [thickness or a break], B-lines, and consolidation (7).

Soldati et al. proposed a scoring system for the degree of lung affection by diseases, called the Chest Ultrasound Score that divides the chest areas and gives each area a score from 0 to 3 depending on the degree of affection and the presence of A-lines, B-lines, consolidation, hypoechoic lesion, or white lung, (8); Soldati score could be mixed with modified LUS score proposed by Jean-Jacques Rouby et al to make the total score 36, (9). Some studies have suggested a prognostic value of LUS assessment in patients with COVID-19 pneumonia and its direct relation to the inflammatory markers, the clinical condition of the patients, and its ability to predict the outcome (10). However, further studies are needed to display and augment these clinical implications.

The study aimed to evaluate the role of LUSS in predicting the prognosis and outcome of COVID-19 Pneumonia patients.

Patients and Methods

This is a prospective observational cohort study enrolling 82 patients that was conducted in the isolation unit of our university Hospital from January 2022 to June 2023.

The study was approved by the Institutional Review Board, Faculty of Medicine of Assiut University **(IRB no. 17101631**), and all patients provided informed consent.

As a specialized tertiary referral center, Assiut University Hospital received cases classified as severe or critical according to the WHO classification (11).

WHO classification of COVID-19 pneumonia severity:

<u>Severe</u>: Patient with clinical signs of pneumonia [fever, cough, dyspnea] plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air.

-<u>Critical</u>: Patient with ARDS.

Inclusion Criteria:

1- Patients over 18 years of age.

2- Patients confirmed as COVID-19 pneumonia with PCR.

Exclusion Criteria:

1- Patients under 18 years of age.

2- Patients with negative COVID-19 PCR.

3- Patients with ILD and Bronchiectasis.

All patients underwent **3** rounds of chest ultrasound evaluation, and each patient was given a score according to ultrasound findings. (Modified 12-zone/0–36 score is used in the present study, in which three scores were modified to be consistent with COVID-19 pneumonia patients).

The first round was done upon admission, the second round after 3 days, and the final round after 5 days.

The patient was in an upright or lateral decubitus position; a curvilinear probe was used.

Twelve areas were examined in the Lung Ultrasound Evaluation, and each area was given a score from 0 to 3 according to the findings (total from 0 to 36) in each round of the evaluation. Areas that were examined include:

1-Left Anterior Superior. **2-**Left Anterior Inferior. **3-**Left Lateral Superior. **4-**Left Lateral Inferior. **5-**Left Posterior Superior. **6-**Left Posterior inferior. **7-**Right Anterior Superior. **8-**Right Anterior Inferior. **9-**Right Lateral Superior. **10-**Right Lateral Inferior. **11-**Right Posterior Superior. **12-**Right Posterior inferior (12).

Classification of score (8):

Score 0: Regular pleural line. Horizontal artifacts -A lines- are present.

Score 1: The pleural line is indented. Below the indent, vertical white areas are visible.

Score 2: Below the breaking point, consolidated regions of varying sizes [darker areas] emerge, accompanied by white areas beneath the consolidated sections.

Score 3: The scanned area shows dense and largely extended white lung (the coalescence of many vertical artifacts) **(Figure 1**).

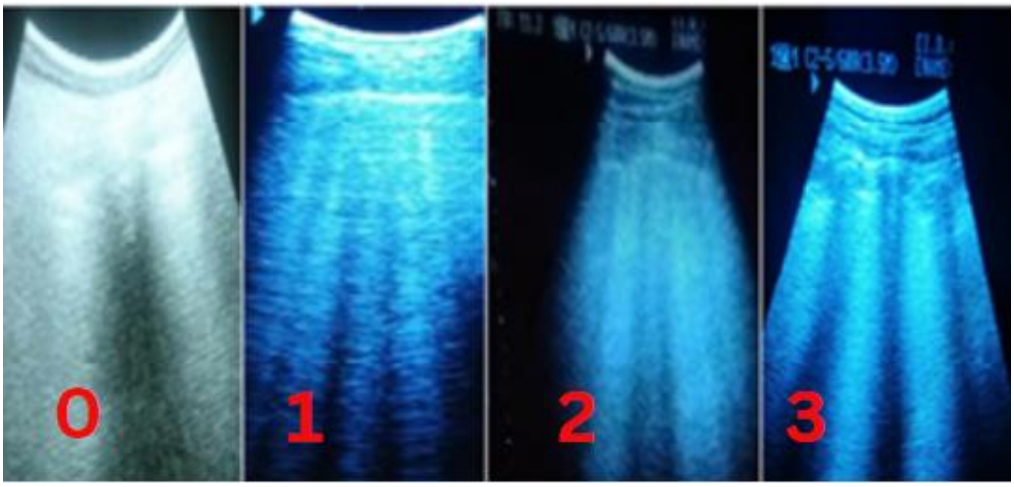

Figure1: Lung Ultrasound Score Classification.

In the present study, patients were divided into two groups according to the cut-off value chosen in the Ji et al study, a low-score group with 12 or fewer points and a high-score group with more than 12 points, 30 patients (36.6%) had low scores and 52 patients (63.4%) had high scores (13) (**Figure 2**).

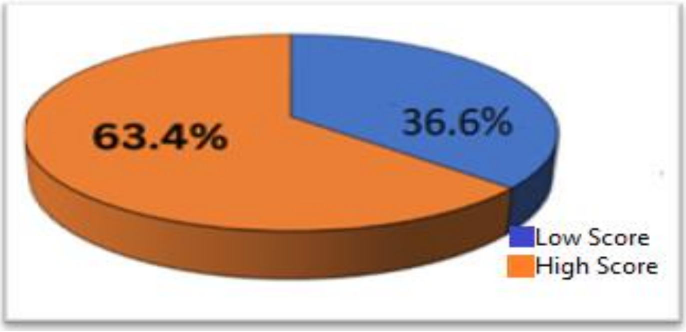

Figure 2: Patients' classification according to LUSS with **12** as a cut-off point

With every round of Lung Ultrasound, the clinical data, including conscious level, oxygenation, need for ventilatory support, and other vital signs and laboratory investigations, including Complete Blood Count, Kidney function, Liver function, P.T, P.C, INR, inflammatory markers such as D-Dimer, CRP, LDH at that time were recorded.

Statistical analysis sample size calculation:

Sample size calculation was carried out using G*Power 3. A minimum calculated sample of 60 COVID-19 cases was needed to detect an effect size of 0.2 (22%-70%) vs (40%-93%] in the diagnostic yield (sensitivity and specificity) of lung US in the severity of COVID-19 diagnosis, with an error probability of 0.05 and 80% power on a one-tailed test. The present study achieved 136% of the targeted statistically significant sample size (14).

Statistical analysis was done using SPSS (Statistical Package for the Social Sciences, version 20, IBM). The Shapiro test determined the data's compliance with normal distribution. Quantitative data with normal distribution are expressed as mean ± standard deviation (SD) and compared with the Student t-test (15)(16).

Nominal data are numbers (n) and percentages (%). Chi test was implemented on such data (17). The accuracy of the lung ultrasound score in predicting the disease's severity, disease progression, and mortality was determined by the receiver operator characteristic (ROC) curve. The confidence level was kept at 95%; hence, the *P* value was considered significant if < 0.05.

Results

Baseline characteristics of patients' data are shown in **Table 1.**

Table 1: Baseline characteristics of patients' data

Characteristic	
Age (years)	
Total [mean ± SD]	63.4 ± 12.4
< 60 N [%]	26 [31.71%]
> 60 N [%]	56 [68.29%]
Sex	
Male N [%]	36 [42.68%]
Female N [%]	46 [56.09%]
Comorbidities	
Diabetes mellitus N [%]	30 [36.5%]
Hypertension N [%]	9 [10.9%]

N: Number of patients

Forty patients (51.2%) had a severe infection, and 40 patients (48.8%) had a critical infection (**Figure 3).**

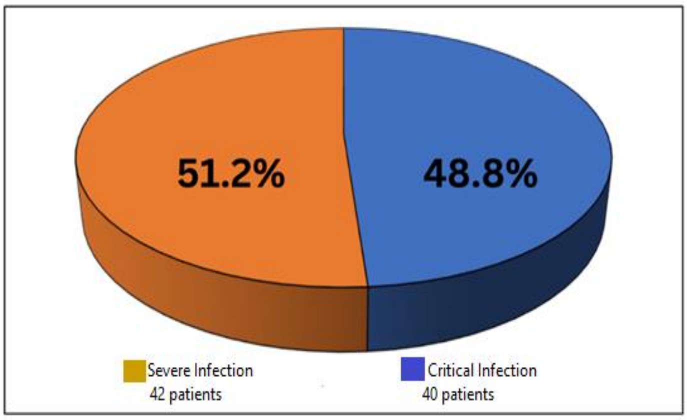

Figure 3: Distribution of patients based on disease severity

47 (57.3%) patients improved, while 35 (42.7%) deteriorated and died**.** Regarding clinical and laboratory data based on lung ultrasound scores, Patients with high scores had more significantly impaired oxygen saturation than those with low scores (88.60 ± 9.43 vs 71.45 ± 17.98) and a P value of < **0.001**. Patients with high LUSS had significantly higher LDH (567.28 ± 55.09 vs. 345.74 ± 43.45 [u/l]; *p* < 0.001), CRP (110.35 ± 85.24 vs. 69.41 ± 73.33 mg/dl; *p* < 0.001) and ferritin (1272.45 ± 143.76 vs. 615.84 ± 75.47 ng/ml; *p* < 0.001) and lower lymphocytes (0.81 ± 0.61 vs. 1.25 ± 0.75 (10^3/ul); *p*< 0.001) Clinical data and laboratory data based on lung ultrasound score with a cut-off point of 12 are shown in **Table 2.**

Table 2: Clinical data and laboratory data based on lung ultrasound score [cut-off point of 12]

	Low Score [n=30]	High Score [n=52]	P value
Heart rate [beat/min]	92.20±12.19	96.13±14.61	0.12
Respiratory rate [cycle/min]	32.53±3.48	34.14±3.83	0.06
Oxygen saturation [%]	88.60±9.43	71.45±17.98	< 0.001
Laboratory data			
Leucocytes [10^1/ul]	9.90±4.97	10.01±6.45	0.11
Lymphocyte [10^1/ul]	1.25±0.75	0.81±0.61	< 0.001
Hemoglobin [g/dl]	12.11±2.01	12.03±2.98	0.07
Hematocnt value [%]	39.13±7.01	37.40±8.03	0.42
Platelets [10^3/ul]	260.98±120.45	254.14±118.91	0.27
INR	1.12±0.21	1.17±0.73	0.98
Urea [mmol/l]	9.94±7.48	10.21±4.11	0.09
Creatinine [mmol/l]	101.94±24.80	108.25	0.30
Albumin [mg/dl]	35.10±5.73	36.97±2.33	0.12
Bilirubin [umol/l]	9.20±3.45	9.82±2.83	0.56
Aspartate transaminase [u/L]	45.96±9.08	50.23±9.22	0.19
Alanine transaminase [u/L]	44.09±11.21	49.83±8.31	0.20
Lactate dehydrogenase [u/L]	345.74±43.45	567.28±55.09	< 0.001
C-reactive protein [mg/dl]	69.41±73.33	110.35±85.24	< 0.001
Ferritin [ng/ml]	615.84±75.47	1272.45±143.76	< 0.001
D-dimer [mg/l]	2.30±0.48	3.49±0.35	0.06

Date expressed as mean [SD]. P-value was significant if < 0.05. n: number of patients; INR: international randomized ratio

Regarding Oxygen therapy and outcome of studied patients based on ultrasound score, it was found that 76.7% of patients with low scores had severe disease while 63.5% of patients with high scores had critical disease, 53.3% of patients with low scores received oxygen therapy through a nasal cannula or venturi mask, 55.8% of patients with high scores required non-invasive or invasive mechanical ventilation; Patients with low scores had significantly shorter hospital stays (8.90 ± 3.48 vs. 20.14 ± 6.11 [days]; $p < 0.001$) in comparison to those with high scores; All patients with low scores improved and were discharged while 67.3% of patients with high scores deteriorated and died, Oxygen therapy and outcome of patients based on ultrasound score with a cut-off point of 12) are shown in T**able 3**.

Table 3: Oxygen therapy and outcome of patients based on ultrasound score [cut-off point of 12]

	Low Score [n=30]	High Score [n=52]	P value
Oxygen therapy			0.04
Nasal canula	16 [53.3%]	21 [40.4%]	
Venturi mask	3 [10%]	2 [3.8%]	
Non-invasive ventilation	4 [13.3%]	2 [3.8%]	
Mechanical ventilation	7 [23.3%]	27 [51.9%]	
Severity of the disease			< 0.001
Non-severe	23 [76.7%]	19 [36.5%]	
Severe	7 [23.3%]	33 [63.5%]	
Outcome			< 0.001
Alive	30 [100%]	17 [32.7%]	
Died	0	35 [67.3%	
Length of stay [days]	8.90±3.48	20.14±6.11	< 0.001

Date expressed as mean [SD], and frequency [percentage]. *P*-value was significant if < 0.05. n: number of patients.

As for the Accuracy of LUSS in predicting disease severity, a cut-off point of> 17 LUS had **79.4%** overall accuracy in predicting severe infection, with the area under the curve of 0.880. The accuracy of LUSS using 17 as a cut-off point in predicting the severity of infection and mortality is shown in **Table 4 (Figure 4).**

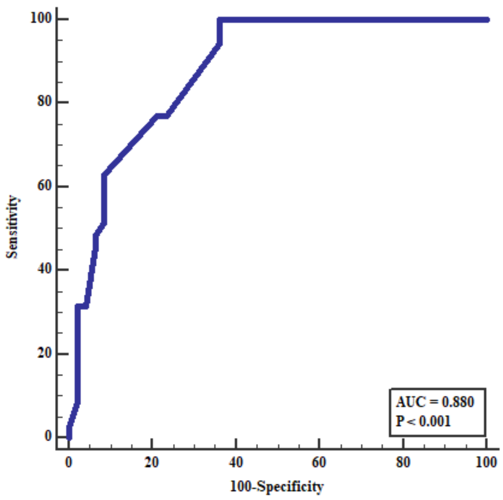

Figure 4: Accuracy of LUSS at admission in the prediction of mortality among patients with COVID-19 pneumonia using a **17**-score as a cut-off point

Table 4: Accuracy of LUSS using 17 as a cut-off point in the prediction of severity of infection and mortality

	Severity	Mortality
Sensitivity	77.42%	100%
Specificity	64.71%	64%
Positive predictive value	66.93%	73%
Negative predictive value	90.32%	100%
Accuracy	79.20%	79.4%

P-value was significant if < 0.05

Regrading the accuracy of serial LUSS in prediction of disease's Prognosis and outcome, by doing a serial LUSS and comparing the LUSS with clinical and laboratory data of the patients at the time of LUSS, out of the 46 patients with clinical improvement, 40 (86.9%) demonstrated a simultaneous reduction in the serial LUSS, out of the 36 cases with clinical deterioration, 30 cases (83.3%) demonstrated simultaneous an increase in serial LUSS; After performing serial LUSS, the accuracy was found to be **80.5%** Accuracy, **86%** Sensitivity, and **75%** Specificity for Prediction of outcome of COVID-19 pneumonia patients. The relationship between LUSS and Disease Outcome is shown in **Table 5.**

Table 5: Relationship between LUSS and Disease Outcome

	Discharge	**Death**	***P-value***
LUSS			
Mean± SD	13.49±1.9	18.91±3.8	0.002*
Median [IQR]	14 [7]	17 [6]	

* Independent Sample t-test was used to compare the mean difference between groups

An Independent Sample t-test was used to compare the groups' mean differences. The relationship between each LUSS and Disease Outcome is shown in **Table 6**

Table 6: Relationship between each LUSS and Disease Outcome

Diagnostic criteria	**1st LUSS**	**2ND LUSS**	***3rd LUSS***
AUC	0.675	0.746	0.826
95% Cl	0.551-0.799	0.636-0.857	0.727-0.926
P-value* **	= 0.007	< 0.001	< 0.001
Accuracy	69 %	75.5 %	80.5%
Sensitivity %	74 %	77 %	86 %
Specificity %	64 %	74 %	75 %
PPV %	67 %	75 %	77.5 %
NPV %	71 %	76 %	84 %
Youden's J	0.38	0.51	0.61

* AUC = Area under the Curve. ** SE=Standard Error. CI = Confidence Interval. *** Null hypothesis: true area = 0.5, Sensitivity [true positives / all diseased]; specificity [true negatives / all non-diseased]; PPV [true positives / all test positives]; NPV [true negatives / all test negatives].

Discussion

Chest ultrasonography is an important tool in assessing COVID-19 pneumonia (6). One of the important applications of ultrasonography is LUSS, a subjective way of assessing patients. Different studies applied different scores to classify patients' clinical conditions; The ultrasonographic score cut-off point that could differentiate between patients' clinical situations varies between studies, mostly due to the score model used and the clinical condition of the sample population (18). Ji L et al used 12 as a cut-off point to determine patients' prognosis (13). In the present study, a score of 12 was also used in differentiating between patients with low scores and high scores; however, further analysis of our results, taking into consideration that our patients' pool consisted only of severe and critical patients, found that 17 was the most accurate score in predicting severity and morality in our sample population. The present study used the modified 36-point score to assess COVID-19 pneumonia (8) (19).

Guerino Recinella et al noted that LUSS of 17 could predict patients with worse outcomes; they also used a 36-point score model similar to the model used in this study (20).

The present study noted a significant association between high LUSS and clinical conditions, with 63.5% of patients with high scores having critical disease and disease progression. This link was also recorded by Song et al., who noted a progressively higher LUSS with disease progression (21).

In the current study, LUSS had good accuracy, sensitivity, and specificity for outcome prediction of COVID-19 pneumonia patients' prognosis, with a Sensitivity of (77.42% and 100%), a Specificity of (64.71% and 64%), and an Accuracy of (79.20% and 79.4%) for severity and mortality, respectively.

Lieveld et al observed that LUSS has high specificity in detecting changes in pulmonary involvement with high prognostic value and high specificity of LUSS (83.3%) (22).

The current study's results concur with those of a study by Zhu et al., who reported that the LUSS score was significantly higher in critically ill patients than in non-critically ill patients and that LUSS has a sensitivity of 81% and a specificity of 96% in predicting the prognosis and outcome of COVID-19 pneumonia (23).

This study also examined the use of serial LUSS, which was found to have **80.5%** accuracy, **86%** Sensitivity, and **75%** Specificity for predicting the outcome of COVID-19 pneumonia patients.

Senter et al. conducted a study in which serial LUSS was performed, and they noted that it had a significant value in predicting patients' prognosis, with increasing LUSS correlating with clinical deterioration (24). Furthermore, Sosa et al. conducted a study in which the LUSS was measured on admission, days 5, and 10. As the clinical condition deteriorated, the LUSS increased (25).

Lung ultrasonography score is also significantly related to patients' gas exchange conditions, as significantly impaired arterial oxygen saturation was observed with increased patient LUSS. These findings concur with the study by Vasseur et al., which found a statistically significant negative linear correlation between patients' oxygenation and LUSS (26).

The current study found that LDH and ferritin are also higher, and the lymphocytic count was lower in patients with higher [R - 0.144; P 0.01]. These results align with the study by Ahmed et al., which found that lymphocytic count was lower and D-dimer, ferritin, and CRP were higher in the more critical patients (27). This reliable correlation between lung ultrasound score and inflammatory markers suggests that LUS might be considered for evaluating acute inflammatory lung diseases.

Conclusion:

LUSS can be used successfully 1- to predict both the prognosis and the outcome of cases with COVID-19 pneumonia and 2- for follow-up of the condition, as it has a high association with the clinical condition of the patient, including the oxygenation, need for ventilatory support, and inflammatory markers.

This has significant clinical real-life application as it produces a quantifiable, reproducible, cheap, safe, and reliable method for evaluating COVID-19 cases without the hazards or financial burden of serial HRCTs.

Limitations:

A) This single-center study included only patients classified as severe or critical according to the WHO classification. B) All the cases were classified as severe or critical, with no mild or moderate cases.

Recommendations:

LUSS should be used regularly to quantify the severity of lung affection in

COVID-19 and evaluate and predict the course of COVID-19 disease.

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Nil.

Conflicts of interest:

There are no conflicts of interest.

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