Use of pulmonary ultrasound to predict in-hospital mortality in patients with COVID-19 infection

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Abstract

Introduction: Lung ultrasound (LUS) implementation in patients with COVID-19 can help to establish the degree of pulmonary involvement, evaluate treatment response and estimate in-hospital outcome. **Objective:** To evaluate the application of a LUS protocol in patients with COVID-19 infection to predict in-hospital mortality. **Methods:** The study was carried out from April 1 to August 1, 2020 in patients with COVID-19 infection admitted to the Intensive Care Unit. Lung evaluation was carried out by physicians trained in critical care ultrasonography. **Results:** Most patients were males, median age was 56 years, and 59 % required mechanical ventilation. In-hospital mortality was 39.4 %, and in those with a LUS score ≥ 19 , mortality was higher (50 %). The multiple logistic regression model showed that a LUS score ≥ 19 was significantly associated with mortality (hazard ratio = 2.55, $p = 0.01$). **Conclusions:** LUS is a safe and fast clinical tool that can be applied at bedside in patients with COVID-19 infection to establish the degree of parenchymal involvement and predict mortality.

KEY WORDS: COVID 19. Lung ultrasound. Mortality.

Uso de ultrasonido pulmonar para predecir mortalidad intrahospitalaria en pacientes con infección por COVID-19

Resumen

Introducción: La implementación del ultrasonido pulmonar (LUS) en los pacientes con COVID-19 puede ayudar a establecer el grado de afectación pulmonar, evaluar la respuesta al tratamiento y estimar el desenlace intrahospitalario. **Objetivo:** Evaluar la aplicación de un protocolo LUS en pacientes con infección por COVID-19 para predecir mortalidad intrahospitalaria. **Métodos:** El estudio se realizó del 1 de abril al 1 de agosto de 2020 en pacientes con infección por COVID-19, ingresados en la Unidad de Terapia Intensiva. Se realizó evaluación pulmonar por médicos entrenados en ultrasonografía crítica. **Resultados:** La mayoría de los pacientes fue del sexo masculino, la edad mediana fue de 56 años y 59 % requirió ventilación mecánica. La mortalidad intrahospitalaria fue de 39.4 % y en aquellos con puntuación de LUS ≥ 19 , de 50 %. El modelo de regresión logística múltiple mostró que la puntuación de LUS ≥ 19 se asoció significativamente a mortalidad (cociente de riesgo = 2.55, $p = 0.01$). **Conclusiones:** El LUS es una herramienta clínica segura y rápida que puede realizarse al lado de la cama de los pacientes con infección por COVID-19, para establecer el grado de afectación parenquimatosa y predecir la mortalidad.

PALABRAS CLAVE: COVID 19. Ecografía pulmonar. Mortalidad.

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Introduction

SARS-CoV-2 is an agent that appeared in December 2019 and that causes COVID-19.¹ It belongs to the same group of RNA viruses that cause serious respiratory diseases such as SARS and MERS.² The main manifestation of SARS-CoV-2 infection is a viral pneumonia that can evolve into severe acute respiratory distress syndrome; therefore, the outbreak of this virus demands more admissions to emergency departments and critical care units, with a high proportion of mechanical ventilation requirement.

The use of lung ultrasonography (LUS) as a diagnostic tool in critically ill patients for establishing the degree of parenchymal involvement, to assess treatment response, and during follow-up is a common practice that has become a high-quality patient bedside standard of care.^{3,4}

Multiple studies have described that computed axial tomography and LUS show an important correlation with the main pulmonary syndromes, such as interstitial syndromes, pneumothorax, lung consolidation and pleural effusion.⁵ LUS implementation may reduce requests for chest X-ray and computed tomography, which is particularly relevant for improving hospital safety policies in order to limit staff exposure to SARS-CoV-2.⁶

Despite the time that has elapsed since the first COVID-19 case in Wuhan, China, working groups all over the world are trying to answer questions about how protocols can increase LUS diagnostic power and provide predictive information on hospital outcomes.⁷ A recent single-center study showed that the observation of increased compromise on LUS predicts mortality and the need for mechanical ventilation;⁸ however, these findings have not been proven elsewhere. The purpose of this study was to evaluate the usefulness of a LUS protocol to predict in-hospital mortality in patients with COVID-19 infection.

Method

This cross-sectional study included 101 adult patients with confirmed COVID-19 infection (by real-time reverse transcription polymerase chain reaction [RT-PCR] for SARS-CoV-2 RNA detection), admitted to the Intensive Care Unit at "Ignacio Chávez" National Institute of Cardiology, Mexico City, between April 1 and August 15, 2020. Evaluation was carried out using the LUS technique indicated in the ORACLE

protocol.⁴ The institutional committee of the Institute approved the investigation. Written informed consent was granted by the patient or a legally authorized representative.

Image acquisition and quantification

The protocol was designed to allow rapid image acquisition at patient bedside, and image analysis was done outside patient rooms. The study was carried out by cardiologists and critical care specialists with experience in ultrasound recording and interpretation in critically ill patients. In all cases, LUS complete evaluation was performed at patient admission to the Intensive Care Unit in less than five minutes. The following measures were applied to minimize staff exposure to infection:

- All studies were performed during regular/routine patient rounds.
- The machine and sector probe were adequately sanitized between each evaluation.
- All personnel had adequate personal protective equipment.
- Measurements were performed outside the patient's room.

The operator obtained the images with a phased array sector probe, at 2 or 3 mHz, from the patient's right or left side, on any platform and with M and 2D modes, with a depth of 10 to 15 cm. The following points were evaluated on each hemithorax, beginning at the right side, with the marker of the probe pointing to the patient's head:

- Anterior-superior: second intercostal space, mid-clavicular line (points 1 and 7).
- Anterior-inferior: fifth intercostal space, midclavicular line (points 2 and 8).
- Lateral-superior: second intercostal space, anterior axillary line (points 3 and 9).
- Lateral-inferior: fifth intercostal space, anterior axillary line (points 4 and 10).
- Posterior-superior: second intercostal space, mid to posterior axillary line (points 5 and 11).
- Posterior-inferior: fifth intercostal space, mid to posterior axillary line (points 6 and 12).

At each point, the following scores were applied, and total sum of 12 points was calculated (Fig. 1):

- 0, A-profile: presence of A-lines with less than three B-lines.
- 1, B-profile: presence of three or more B-lines with > 3-mm separation.

Figure 1. Exploration points and most common findings at each region.

- 2, B-profile: presence of three or more B-lines with ≤ 3 -mm separation.
- 3: C-profile: consolidation, shred sign, or A/B-profile.⁴

To determine the RALE score, each radiograph was divided into quadrants, vertically defined by the spinal column and horizontally by left main bronchus first branch. Each quadrant was assigned a 0-4 consolidation score to quantify the extent of alveolar opacities. To calculate RALE final score, the product of the consolidation score of each quadrant was added.⁹ The RALE score was calculated by a specialist in cardio-pulmonary medicine.

Statistical analysis

The Shapiro-Wilk normality test was used for continuous variables; after knowing their distribution, variables were recorded with the mean and standard deviation if they were parametric, and median and interquartile range (IQR) were used if they were non-parametric. Continuous variables were compared with Mann-Whitney's U-test. Categorical variables were described with frequencies and percentages; the chi-square test and Fisher's exact test were used for comparisons, as appropriate, according to the expected values.

In order to establish a cutoff point for B-lines, the ROC analysis was used, in which 19 or more B-lines yielded the highest sensitivity, specificity, and predictive probability. A logistic regression model, adjusted

for age and gender, was created to find out the variables that predicted mortality. Mortality between groups was compared with Kaplan-Meier plots. All statistical analyses were considered significant with a p-value < 0.05. Statistical analyses were performed using STATA, version 14.

Results

Clinical data were collected from 101 consecutive patients with confirmed COVID-19 infection.

Most patients were males (76.2 %), with a median age of 56 years (IQR = 48-65), and most common comorbidities were hypertension and type-2 diabetes (38 and 33 %, respectively). Median partial pressure of oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) was 190. Patients were hemodynamically stable at admission, with a median heart rate of 80 (70-92) bpm, systolic blood pressure of 125 (110-134) mmHg and diastolic blood pressure of 74 (67-80) mmHg. Laboratory tests revealed elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), D-dimer, C-reactive protein, and ferritin at admission. Median RALE score was 6 (Table 1). Mechanical ventilation was required by 59 % of patients, and hospital mortality was 39.4 %; in patients with a LUS score ≥ 19 , mortality was higher (50 %) than in those with a score < 19 (Table 2). In a sub-analysis, only superinfection (hazard ratio [HR] = 3.42, p = 0.001) predicted the need for mechanical ventilation.

Table 1. Clinical and demographic characteristics

Variable	Total		LUS score				p
			< 19		≥ 19		
	n	(%)	n	(%)	n	(%)	
Males	77	76.2	33	73.3	44	78.6	0.64
Females	24	23.8	12	26.7	12	21.4	0.64
Hypertension	38	37.6	19	42.2	19	33.9	0.39
Diabetes mellitus	33	32.7	17	37.8	16	28.6	0.32
Smoking	30	29.7	16	35.6	14	25	0.24
Dyslipidemia	17	16.8	9	20	8	14.3	0.44
	Median	IQR	Median	IQR	Median	IQR	
Age, years	56	48-65	57	50-63	56	47-66	0.85
PaO ₂ /FiO ₂	198	145-260	200	156-260	190	142-257	0.75
– Heart rate, bpm	80	73-92	80	75-88	88	70-95	0.24
– Systolic blood pressure, mmHg	125	110-134	128	110-133	124	113-135	0.77
– Diastolic blood pressure, mmHg	74	67-80	75	65-80	74	67-81	0.76
Troponin I at admission, pg/mL (14-42.9 pg/mL)	15	7-58	22	7.7-73	14	6-44	0.30
Troponin I peak (pg/mL)	93	23-265	123	24-354	83	20-238	0.39
D-dimer at admission (ng/mL) (< 500 ng/mL)	610	272-1732	590	271-2,588	610	272-1,420	0.74
D-dimer peak (ng/mL)	1890	690-5,620	3,555	690-8,084	1450	720-2,855	0.20
NT-proBNP at admission, pg/mL (15-125 pg/mL)	759	220-3475	716	299-4,058	900	205-3,261	0.97
NT-proBNP peak, pg/mL	1114	409-7,004	943	409-5,367	1,186	339-7,004	0.77
Creatinine at admission, mg/dL	0.9	0.7-1.45	0.9	0.7-1.8	0.9	0.6-1.2	0.69
Creatinine peak, mg/dL	1.2	0.9-2.7	1.1	0.9-2.9	1.3	0.9-2.6	0.79
C-reactive protein at admission, mg/dL (1-3 mg/L)	128	61-246	119	42-209	136	66-262	0.43
C-reactive protein peak, mg/dL	261	139-346	239	137-321	278	147-362	0.32
Ferritin at admission, mg/dL (23.9- 336 ng/mL)	744	409-1306	784	430-1,110	667	366-1,352	0.91
Ferritin peak, mg/dL	1,069	560-2,000	955	540-1,470	1224	656-2,000	0.13
RALE score	6	4-7	6	4-7	6	4-7	0.67

IQR = interquartile range NT-proBNP = N-terminal pro-B-type natriuretic peptide.

A LUS median score of 19 points was documented. Figure 1 depicts the most common finding at each lung ultrasound point. The multiple logistic regression model for the prediction of mortality showed that a LUS score ≥ 19 was significantly associated with the result (HR = 2.55, $p = 0.01$) (Table 3). In patients with

a LUS score ≥ 19 , hospital mortality was significantly higher (log-rank $p = 0.006$) (Fig. 2).

In the multiple logistic regression model, mechanical ventilation (HR = 3.2, $p = 0.03$), troponin I > 20 pg/mL (HR = 2.1, $p = 0.02$) and NT-proBNP > 800 pg/mL (HR = 2.55, $p = 0.02$) predicted mortality (Table 3).

Table 2. In-hospital outcomes

Variable	Total		LUS score				p
			< 19		≥ 19		
	n	%	n	%	n	%	
Mechanical ventilation	59	58.4	22	48.9	37	66.1	0.10
Death	39	39.4	12	26.7	27	50	0.01
Other infection	11	10.9	4	8.9	7	12.5	0.75
	Median	IQR	Median	IQR	Median	IQR	
Days on mechanical ventilation	6	0-15	0	0-18	8	0-14	0.55
Hospitalization days	15	10-24	17	11-26	13	10-21	0.20

IQR = interquartile range.

Table 3. Multiple logistic regression model for mortality prediction

Variable	HR	SE	p	95 % CI
Age	1.02	0.01	0.12	0.99-1.05
Male gender	1.08	0.43	0.84	0.49-2.38
Hypertension	1.42	0.51	0.32	0.70-2.90
Diabetes	1.02	0.36	0.94	0.51-2.04
Mechanical ventilation	3.21	1.73	0.03	1.11-9.27
Other infection	2.09	0.94	0.10	0.86-5.07
≥ 19 B-lines	2.55	0.93	0.01	1.24-5.23
Troponin > 20 pg/mL	2.16	0.75	0.02	1.09-4.29
NT-proBNP > 800 pg/mL	2.55	1.09	0.02	1.10-5.92
D-dimer > 600 ng/mL	1.12	0.40	0.74	0.55-2.26
C-reactive protein > 100 mg/dL	1.72	0.66	0.16	0.80-3.68
Ferritin > 700 mg/dL	2.09	0.98	0.11	0.833-5.28
RALE score > 6 points	1.06	0.36	0.85	0.54-2.07

HR = hazard ratio, SE = standard error, CI = confidence interval.

Discussion

In our study, we showed that a structured evaluation with LUS and the finding of an elevated score thereof at hospital admission predicted mortality in patients with COVID-19.

As regards clinical variables, there was no significant variation between the presence of a LUS score ≥ 19 and $\text{PaO}_2/\text{FiO}_2$ levels, which suggests that there is already a significant degree of lung parenchymal involvement at admission before oxygenation scores reach critical levels; the same situation occurs with the RALE radiographic score. The clear increase in

Figure 2. Kaplan-Meier plot, where mortality between patients is compared according to LUS scores.

mortality associated with higher parenchymal involvement documented by LUS suggests that early identification of this finding could guide the clinician for a more aggressive treatment to be established upon admission. LUS could help predict outcomes and even the need for patient early transfer to a critical care area.

It should also be highlighted that, on LUS evaluation of the 12 lung ultrasound points, the most common finding in all cases was the presence of B-profile, which suggests an interstitial process as the main pathophysiological mechanism of the disease, with a low frequency of lung consolidations and pleural effusion. Other secondary findings suggest that mechanical ventilation and elevated cardiac biomarkers (troponin I and NT-proBNP) are also associated with adverse outcomes. None of the physicians who performed the ultrasound became infected, which was confirmed by two viral tests (nasal swab viral nucleic acid identification by RT-PCR and IgG antibodies test).

LUS has several advantages:

- It is available in most centers.
- It is quickly performed.
- The required learning curve is relatively short.
- It allows multiple lung regions assessment to be carried out.
- It limits the risk of exposure of medical staff and other healthcare personnel.
- It decreases patient mobilization from hospital bed.
- It shows an impact on the prediction of adverse outcomes.

For the above reasons, we consider LUS as an invaluable tool in the diagnosis and follow-up of patients with COVID-19 and lung parenchymal disease.

Limitations

This study was conducted in a single hospital center. On the other hand, patients who survived should undergo follow-up in order to assess mortality and long-term complications after discharge, as well as the degree of lung sequelae.

Conclusion

LUS is an easily accessible, safe, and quick-to-perform clinical tool that can be carried out at patient bedside. A high LUS score helps to predict in-hospital mortality.

We propose for this test to be routinely applied in COVID-19 patients in order to predict the outcome, establish an aggressive therapy, and aid early admission to a critical care unit.

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Conflict of interests

The authors declare that they have no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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