European Review for Medical and Pharmacological Sciences 2021; 25: 3623-3631

Clinical application of lung ultrasound score on COVID-19 setting: a regional experience in Southern Italy

M. LUGARA[1], G. OLIVA[1], P.C. PAFUNDI[2], S. TAMBURRINI[3], R. NEVOLA[2], K. GJELOSHI[2], C. RICOZZI[2], S. IMBRIANI[2], A. PADULA[2], C. APREA[2], L. MEO[2], D. COZZOLINO[2], G. CUOMO[2], A. MARRONE[2], C. ROMANO[2], V. FIORINI[3], M.G. COPPOLA[1], M. CORVINO[4], A. PERRELLA[5], G. PONTI[6], G. NUNNARI[7], R. RANIERI[8], C. RUOSI[8], F.C. SASSO[2], L.E. ADINOLFI[2], L. RINALDI[2]

[1]U.O.C. Internal Medicine, ASL Center Naples 1, P.O. Ospedale del Mare, Naples, Italy
[2]Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy
[3]UOC Radiology, ASL Center Naples 1, P.O. Ospedale del Mare, Naples, Italy
[4]Health Management, ASL Center Naples 1, P.O. Ospedale del Mare, Naples, Italy
[5]Infectious Diseases at Health Direction, AORN A. Cardarelli, Naples, Italy
[6]Department of Surgery, Medicine, Dentistry and Morphological Sciences with Interest in Transplantation, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy
[7]Department of Clinical and Experimental Medicine, University of Messina, Italy
[8]Department of Translational Medical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy

Abstract. – OBJECTIVE: We aimed to assess the correlation between LUS Soldati proposed score and clinical presentation, course of disease and the possible need of ventilation support/intensive care.

PATIENTS AND METHODS: All consecutive patients with laboratory confirmed SARS-CoV-2 infection and hospitalized in two COVID Centers were enrolled. All patients performed blood gas analysis and lung ultrasound (LUS) at admission. The LUS acquisition was based on standard sequence of 14 peculiar anatomic landmarks with a score between 0-3 based on impairment of LUS picture. Total score was computed with their sum with a total score ranging 0 to 42, according to Soldati LUS score. We evaluated the course of hospitalization until either discharge or death, the ventilatory support and the transition in intensive care if needed.

RESULTS: One hundred and fifty-six patients were included in the final analysis. Most of patients presented moderate-to-severe respiratory failure (FiO_2 <20%, PaO_2 <60 mmHg) and consequent recommendation to invasive mechanic ventilation (CPAP/NIV/OTI). The median ultrasound thoracic score was 28 (IQR 18-36) and most of patients could be ascertained either in a score 2 (40%) or score 3 pictures (24.4%). The bivariate correlation analysis displayed statistically significant and high positive correlations between the LUS score and the following parameters: ventilation (rho=0.481, p<0.001), lactates (rho=0.464, p<0.001), dyspnea (rho=0.398, p=0.001) mortality (rho=0.410, p=0.001). Conversely, P/F (rho= −0.663, p<0.001), pH (rho = −0.363, p=0.003) and pO_2 (rho = −0.400 p=0.001) displayed significant negative correlations.

CONCLUSIONS: LUS score improve the workflow and provide an optimal management both in early diagnosis and prognosis of COVID-19 related lung pathology.

Key Words:
Lung ultrasound, COVID19, LUS score, Intensive care, Blood gas analysis.

Introduction

The SARS-COV-2 infection (COVID-19) determining Severe Acute Respiratory Syndrome represented a serious challenge to public health, especially in the emergency department (ED) for almost one year[1-2]. COVID-19 clinical presentations may vary from mild/asymptomatic to critical illness, being characterized by acute respiratory failure, according to different clinical presentation[3]. Although standard imaging methods still remain a gold standard, point-of-care

Corresponding Author: Luca Rinaldi, MD; e-mail: luca.rinaldi@unicampania.it

ultrasound (POCUS) has been revealing to be a unique faster, safer and costs-saving strategy for both diagnosis and risk stratification of COVID-19 patients[4].

Lung ultrasound (LUS) has remarkably been evolved over the last years with interesting results in internal medicine being able to define the alterations affecting the ratio between tissue and air in the superficial lung[5,6]. Usually, lung surface mainly consists of air, with incident ultrasound (US) waves generally completely reflected by the visceral pleural plane, especially in healthy people. In this context, the scattering of US waves produces artifactual images with typical horizontal reverberations of the pleural line (A-lines) and mirror effects. When the contact between air, tissue, fluid, or other biological components is reduced, lungs no longer serve as a specular reflector[7]. Hence, various types of localized vertical artifacts appear on the US images in relation to the alterations of the subpleural tissue, commonly called as B-lines, whose heterogeneity may be exploited as a way to characterize the alterations of the lung surface[8]. The study of these patterns displays a very high sensitivity in cases of interstitial and alveolar-interstitial lung diseases, which have a peripheral distribution, as confirmed by some studies[9,10] on acute respiratory distress syndrome (ARDS) in COVID-19 disease setting.

Despite Computed Tomography (CT) represents the gold standard in the lung imaging, the role of LUS may acquire a relevant role in the context of the COVID-19 pandemic. Therefore, LUS capability to identify changes in the physical state of superficial lung tissue, may be useful to correlate to possible histopathologic alteration, as well as their evolution or regression over time, determining clinical presentation. Further, in experimental models of ARDS, LUS has been proven to be able to detect lung lesions before the development of hypoxemia[11-13].

Recently, an Italian study group has proposed a standardization for the international use of LUS for the management of COVID-19 patients in order to validate the terminology related to image artifacts and to adopt objective clinical standards for their interpretation. In this view, Soldati et al[14] have computed a specific LUS score.

In this brief report, we describe our experience with lung ultrasonography in a COVID-19 setting, looking more in depth at correlations between Soldati LUS Score and the severity of hospital course.

Patients and Methods

Patients

This prospective observational cohort study involved consecutive patients admitted to two COVID Centers in the South of Italy (Campania region), "Ospedale del Mare" and University of Campania Luigi Vanvitelli, respectively. We included only adult patients (≥ 18 years) with laboratory confirmed SARS-CoV-2 infection, hospitalized in the period between November 15, 2020 and January 31, 2021. SARS-CoV-2 diagnosis was performed by nucleic acid test by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR), obtained either by a nasal or oropharyngeal swab.

All patients were evaluated and treated in a dedicated room. Anamnestic, epidemiological and demographic data were recorded either from the patients themselves or from their families. As

Clinical phenotypes	1	2	3	4
Clinical features	• Fever • Mild respiratory symptoms • No hypoxemia (normal ABG and 6-MWT) • Normal CXR.	• Fever • Mild hypoxemia • Infiltrates on CXR.	• Fever • Moderate to severe respiratory failure • Need of CPAP/NIV.	• Severe respiratory failure from ARDS **or** • Complicated pneumonia • Need of CPAP or invasive ventilation.

Figure 1. Clinical phenotypes of COVID-19 infection.

well, also all symptoms, whether present (e.g., fever, cough, dyspnea, diarrhea), comorbidities, basal biochemistry, were recorded.

We classified the patients in four subgroups based on the different severity of symptoms (phenotypes 1-4) (Figure 1). We evaluated the course of hospitalization until either discharge or death, the ventilatory support and the transition in intensive care, if needed, based on the degree of respiratory failure. Given that only 4.4% of patients required intubation, we merged the patients undergoing invasive and non-invasive ventilation into a single group in order to have a statistically more suitable comparison.

The administered pharmacological therapies and any collateral effect were further collected.

The study was approved by local Ethics Committee and is in accordance with 1976 Declaration of Helsinki and its later amendments. All patients gave their written consent.

Laboratory and Blood Analysis Test

Venous blood samples were collected mainly to assess inflammatory indices, blood counts, renal and hepatic function.

All patients performed blood gas analysis at admission, performed at the radial artery. The oxygenation status was assessed by O_2 partial pressure value (pO_2), CO_2 partial pressure value (pCO_2) and hemoglobin oxygen saturation (SO_2). We used the P/F ratio to compare different values of arterial pO_2 in patients receiving different fraction of inspired oxygen (FiO_2). P/F ratio was obtained dividing the pO_2 by the percent of FiO_2, expressed as decimals. Moreover, we computed pH and bicarbonate concentration (HCO^{3-}) to evaluate acid-base disorders. Finally, lactate levels were also recorded to evaluate possible degree of tissue necrosis.

Lung Ultrasound

All patients underwent to lung ultrasound examination on admission in emergency or in a COVID ward within 3 days from the onset of symptoms. LUS were performed by four expert operators in each Center (trained by a dedicated Course and previous clinical practices in LUS) blinded for any other imaging technique or clinical data. The acquisition was based on standard sequence of 14 peculiar anatomic landmarks in sitting position (three posterior, two lateral and two anterior for each hemithorax) using a progressive numbering starting from right posterior basal regions. We used either high frequency probe (8-15 mHz) and low frequency probe (2-5 mHz).

The findings were classified according to the Soldati scoring proposed method[14], ranging 0 to 3:

Score 0: the pleural line is continuous and regular, with presence of horizontal artifacts, usually referred to as A-lines.

Score 1: indented pleural line. Below the indent, vertical areas of white, due to local alterations in the acoustical properties of the lung.

Score 2: The pleural line is broken. Below the breaking point, we observe small-to-large, consolidated areas (darker areas) with associated areas of white below the consolidated area (white lung). Beyond consolidations, the appearance of areas of white lung establishes the presence of areas not yet fully de-aerated, where air inclusions are still present but embedded in tissue-like material.

Score 3: the scanned area also shows dense and largely extended white lung either with or without larger consolidations.

The total score was computed with their sum observed in each region, with a total score ranging 0 to 42, according to Soldati LUS score[14-15].

End Point of Study

The primary endpoint was the correlation between LUS score, the course of disease and the possible need of ventilation support/intensive care.

Statistical Analysis

Categorical data were expressed as number and percentages, whilst continuous variables either as mean and standard deviation (SD) or median and interquartile range (IQR), according to their distribution, previously tested by the Shapiro-Wilk test.

The degree of association between Ultrasound thoracic score and other parameters were calculated using Spearman correlation coefficient. A p-value <0.05 will be considered as statistically significant. All analyses were performed by SPSS software (IBM, Armonk, NY, USA), version 24.

Results

One hundred and fifty-six consecutive patients positive for COVID-19 were included in the final analysis, mainly males (64.4%), with a median

Table I. Anthropometric, demographic, clinical and laboratory characteristics of the study population (n=156).

Parameters	
Age (years), median [IQR]	73 [59.5-78]
Sex, n (%)	
M/F	100 (64.4)/56 (35.6)
Signs and Symptoms	
Presence of fever, n (%)	125 (80)
Presence of cough, n (%)	125 (80)
Hyperemia pharyngeal, n (%)	66 (42.2)
Asthenia, n (%)	90 (57.8)
Vomiting, n (%)	17 (11.1)
Diarrhea, n (%)	34 (22.2)
Dyspnea, n (%)	121 (77.8)
Tachycardia, n (%)	111 (71.1)
Phenotype, n (%)	
Type 1	21 (13.3)
Type 2	49 (31.1)
Type 3	69 (44.4)
Type 4	17 (11.1)
Pre-existing comorbidities	
Hypertension, n (%)	142 (91.1)
Diabetes mellitus, n (%)	52 (33.3)
Atrial fibrillation, n (%)	10 (6.7)
Ischemic heart disease, n (%)	52 (33.3)
Ictus, n (%)	10 (6.7)
Dementia, n (%)	45 (28.9)
Chronic obstructive pulmonary disease (COPD), n (%)	80 (51.1)
Active cancer in the last five years, n (%)	17 (11.1)
Smoke, n (%)	80 (51.1)
Obesity, n (%)	73 (46.7)
Chronic liver disease, n (%)	7 (4.4)
Chronic Kidney Disease, n (%)	66 (42.2)
Mortality, n (%)	40 (25.6)
Pulmonary embolism, n (%)	7 (4.7)
Days of hospitalization, median [IQR]	15 [5-30]
Ultrasound thoracic, median [IQR]	28 [18-36]
Ultrasound Score, n (%)	
Score 0	3 (2.2)
Score 1	28 (17.8)
Score 2	62 (40)
Score 3	38 (24.4)
Missing	24 (15.6)
Oxygen interface, n (%)	
Nasal cannula/glasses	56 (35.6)
Venturi Mask	59 (37.8)
CPAP/Bi-level	34 (22.2)
Orotracheal Intubation	7 (4.4)

Abbreviations: IQR: Interquartile Range; SD: Standard Deviation; M: Male; F: Female; BMI: Body Mass Index.

age of 73 years (IQR: 59.5-78 years). Demographic characteristics are listed in Table I.

On admission, the most common symptoms were fever (80%) and cough (80%), followed by dyspnoea (77.8%) and tachycardia (71.1%), whilst vomiting and diarrhoea were less frequent.

Most of hospitalized patients presented either a type 2 (31.1%) or a type 3 COVID-19 phenotype (44.4%), this latter characterized by moderate-to-severe respiratory failure (PaO_2 <60 mmHg, P/F <200) and multiple lung thickenings and consequent recommendation to non-invasive or invasive mechanic ventilation (CPAP/NIV/OTI).

As for pre-existing comorbidities, almost all of patients were affected by hypertension (91.1%), whilst almost half of the study population had Chronic obstructive pulmonary disease (COPD; 51.1%), were obese (46.7%) and smoker (51.1%).

The 42.2%, indeed, is affected by Chronic Kidney Disease (CKD).

Moreover, consistent with the phenotypes of disease observed, almost the 60% of patients were either under Venturi mask or CPAP/BiLevel oxygen therapy, whilst only the 4.4% required orotracheal intubation (OTI). As for the biochemical panel (Table II), patients were characterized by a marked lymphopenia (mean lymphocytes count 801.21), altered levels of glycemia (mean 114.8 mg/dL), iron profile, as well as of fibrinogen, d-dimer, NT-proBNP, troponin and procalcitonin.

As for ultrasound evaluation, the median ultrasound thoracic score was 28 (IQR 18-36) and most of patients could be ascertained either in a score 2 or score 3 pictures per scan (40% and 24.4%, respectively) (Figure 2).

The relationship between LUS score and the other parameters recorded in our COVID-19 study population was assessed by the Spearman correlation coefficient.

The bivariate correlation analysis displayed statistically significant and high positive correlations between the composite LUS score and the follow-

Table II. Laboratory characteristics of the study population (n=156).

Parameters	
Laboratory	
Hb (mg/dL), mean (SD)	11.91 (2.4)
White blood cells ($\times 10^3$), median [IQR]	8150 [4975-10050]
Lymphocytes (a.v.), mean (SD)	801.21 (346.17)
Neutrophils (a.v.), median [IQR]	6615 [4525-8635]
Platelets, median [IQR]	177000 [144500-255500]
BUN (mg/dL), median [IQR]	49.50 [37.25-80.50]
Creatinine (mg/dL), median [IQR]	1.01 [0.70-1.79]
Sodium (mmol/L), median [IQR]	140 [135.8-142.3]
Potassium (mmol/L), mean (SD)	4.18 (0.62)
AST (U/L), median [IQR]	27 [16.25-46.75]
ALT (U/L), median [IQR]	24 [15.25-42.25]
Glycemia (mg/dL), mean (SD)	114.8 (41.6)
CRP (mg/dL), mean (SD)	8.70 (7.35)
INR, median [IQR]	1.15 [1.08-1.20]
aPTT (sec), mean (SD)	33.88 (5.35)
Fibrinogen (mg/dL), mean (SD)	466.62 (144.24)
NT-proBNP (pg/mL), median [IQR]	2000 [920-6840]
D -Dimer (pg/mL), median [IQR]	2430 [885-4495]
LDH (mU/mL), mean (SD)	401.88 (146.65)
Troponin (ng/mL), mean (SD)	0.18 (0.65)
Procalcitonin (ng/mL), mean (SD)	2.35 (5.42)
Ferritin (ng/mL), median [IQR]	442 [239.5-629]
Iron (µg/dL), mean (SD)	43.75 (19.97)
CPK (U/L), median [IQR]	109 [30-190]
Blood Gas Analysis	
pH, mean (SD)	7.45 [7.43-7.47]
pO_2 (mmHg), mean (SD)	74.95 (27.65)
pCO_2 (mmHg), mean (SD)	36 [30.15-39.50]
HCO^{3-} (mmol/L), mean (SD)	24.51 (3.64)
spO_2 (%), mean (SD)	94 [89-97]
Lactates (mmol\L), mean (SD)	1.25 [1-2]
FiO_2 at admission, median [IQR]	0.24 [0.21-0.33]
P/F, median [IQR]	250 [157.7-308.9]

Abbreviations: IQR: Interquartile Range; SD: Standard Deviation; Hb: hemoglobin; PLT: platelets; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; CRP: C-reactive protein; LDH: lactate dehydrogenase; CPK: Creatine phosphokinase. *Reference ranges:* Hb - F=12-16/ M=12-18 g/dL; WBCs: 4500-11000, Neutrophils: 1500-7000; Lymphocytes: 1500-7000; PLT: 150000-450000; BUN: blood urea nitrogen; 15-50 mg/dL; Serum Creatinine: 0.51-0.95 mg/dL; Sodium: 135-145 mmol/l; Potassium: 3.5-5 mEq/l; AST (F=8-43 U/L - M=8-48 U/L); ALT (F=7-45 U/L - M=7-55 U/L); Glycemia: 60-110 mg/dL; CRP: 5-10 mg/dL; INR: 0.9-1.3; aPTT: 28-40 sec; Fibrinogen: 200-400 mg/dL; NT-proBNP: ≤ 900 pg/mL; D -Dimer: < 500 pg/mL; LDH: 80-300 mU/mL; Troponin: <0.1; procalcitonin: 0-1; ferritin: M:20-200 ng/mL - F: 20-120 ng/mL; Iron: M: 31-144 µg/dL - F: 25-156 µg/dL; CPK: 60-190 U/L. *Blood gas ranges:* pH: 7.35-7.45; pO_2: 80 -100 mmHg; pCO_2: 35 -45 mmHg; HCO^{3-}: 22 -26 mmol/L; spO^2: 95%-100%; Lactates: <2 mmol/L.

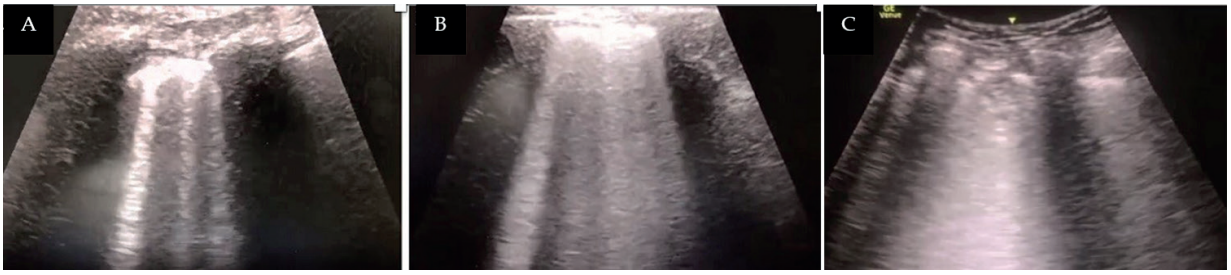

Figure 2. LUS imaging related to score 1 **(A)**, 2 **(B)**, 3 **(C)**.

ing parameters: ventilation (rho=0.481, $p<0.001$), lactates (rho=0.464, $p<0.001$), COVID-19 phenotype (rho=0.527, $p<0.001$), tachycardia (rho=0.411, $p=0.001$), dyspnea (rho=0.398, $p=0.001$) and mortality (rho=0.410, $p=0.001$). These positive correlations demonstrated that a higher composite LUS score corresponds to a higher mortality rate and a more severe COVID-19 phenotype. As well, there was a direct proportionality between an increase in LUS score and elevated lactates levels and need for ventilation. Correlations with age (rho=0.275, $p=0.023$) and d-dimer (rho=0.247, $p=0.044$), indeed, though statistically significant, were remarkably lower. Conversely, P/F (rho= –0.663, $p<0.001$), pH (rho = –0.363, $p=0.003$) and pO_2 (rho = –0.400 $p=0.001$) instead displayed significant negative correlations, which means that a higher LUS scores corresponded to decreased levels of both pH and pO_2. However, the most relevant and clinically important inverse proportionality regards P/F, i.e., a decrease in P/F levels is indicative of higher levels of LUS score. All data are shown in Table III.

Discussion

COVID-19 pandemic is characterized by a variety of signs and symptoms, which make challenging both its management and treatment[16]. Whilst patients with mild disease may show signs of recovery after the first week, others may display either persistent symptoms or organ deteriorations rapidly thereafter[17]. The most characteristic clinical course of severe COVID-19 patients is the development of ARDS. Despite such intensive efforts, ARDS was burdened with a significant rate of mortality[18].

In this perspective, LUS has becoming a clinical practice tool for risk prediction in COVID-19

Table III. Univariate analysis about relationship between Ultrasound thoracic score and other parameters in patients infected by COVID-19.

Parameters	Correlation coefficient	*p*
Age (years)	0.275	0.023
Dyspnea	0.398	0.001
Tachycardia	0.411	0.001
COVID-19 phenotype	0.527	< 0.001
Dementia	0.147	0.235
Platelets	-0.157	0.205
Prothrombin time	0.015	0.902
NT-proBNP	0.144	0.402
D-Dimer	0.247	0.044
pH	-0.363	0.003
pO_2	-0.400	0.001
spO_2	-0.113	0.366
P/F	-0.663	< 0.001
Death patients	0.410	0.001
Ventilation	0.481	< 0.001
Lactates	0.464	< 0.001

setting, thanks to its possibility to be performed bedside, the low cost, absence of radiations, and noninferiority to CR, which indeed could not detect abnormalities in the early phase of illness[19].

Based on our findings, most patients had disease phenotypes 2 and 3, with hypoxia and a prevalence of comorbidities related to respiratory problems (e.g., COPD). The prevalence of more advanced phenotypes indicates a tendency to a late hospitalization, often being in an already advanced lung condition, chronic inflammation and possible interference with respiratory mechanics[20].

As expected, the onset clinical picture was characterized by the alteration of inflammatory parameters, including fibrinogen, d-dimer, NT-proBNP (brain natriuretic peptide), troponin and procalcitonin. These data detected the prominent role of the inflammatory component in determining the main clinical manifestations with a more severe course. Moreover, in our study population, 60% of patients underwent to intensive care accordingly with the prevalence of phenotype 3 (44%).

We also found a significant share of increased glycemic values. Although the hypothesis of an interference of the virus on the insulin activity of pancreatic cells, it seems however that the diagnosis of diabetes is not by itself associated with a worsening prognosis if not related to the presence of obesity and metabolic syndrome[21]. However, a recent meta-analysis[22] on more than 6000 COVID-19 patients with hyperglycemia on admission found a strong increase in the risk of both mortality and several/critical complications. Anyway, the identification of impaired glucose metabolism or new onset diabetes may be useful as it allows the early identification of complications and factors exacerbating the prognosis of the disease[23-25].

The correlation analysis between LUS score and clinical parameters showed a significant direct proportionality with more complicated phenotypes, tachycardia and dyspnea. In addition, both ventilation/intensive care and mortality also significantly correlated with the LUS score, with an inverse proportional trend.

The analysis on blood gas analysis parameters has also revealed very interesting findings. In particular, the inverse correlation between pO_2, pH, P/F and LUS score further confirmed the diagnostic value of this tool. The highly significant correlation of P/F (rho = –0.663, $p<0.001$) is of particular note, as the dynamics of this result provides the most important parameters in the therapeutic management of patients with moderate-to-severe COVID-19. In fact, a ratio between the partial pressure of oxygen and the inspiratory fraction <100 or its non-increase in response to non-invasive ventilation can force to intubation.

Globally, our findings indicated the usefulness of LUS in clinical practice. Moreover, a rapid case identification, classification of disease severity, monitoring disease progression and correct treatment allocation are crucial to enhance care ability, reduce waiting times in the emergency room and initiate drug treatment and/or early ventilatory support. Unfortunately, currently there is no eradicating antiviral therapy for COVID-19 and the only drug currently recommended in the early stages of infection (remdesevir) has demonstrated only a partial efficacy. At the same time, the early use of dexamethasone can help in limiting the onset of the inflammatory cascade[26,27].

Recently, other studies[28,29] have prospectively evaluated the accuracy of the LUS score both on the ability to diagnose COVID-19 in suspected patients[28], and to stratify the risk of invasive mechanical ventilation[29]. In both cases, the results obtained on small series seem promising. In addition, Rubio-Gracia et al[30], in a cohort of 130 COVID-19 patients identified by LUS established a cut-off of 22 as score predictive of in-hospital death and/or admission to the intensive care unit[30]. These recent literature data seem consistent with our findings obtained with the LUS score proposed by Soldati et al[14] especially in the management of hospitalized patients, though these should be validated in a larger population.

Conclusions

The implementation of bedside LUS will vary based on ED volume, availability of resources, and workflows specific to institutional needs. Having an experienced ultrasound team to diagnose and risk-stratify the patients may improve the workflow and provide an optimal management both in early diagnosis and prognosis of COVID-19 related lung pathology.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Galiero R, Pafundi PC, Simeon V, Rinaldi L, Perrella A, Vetrano E, Caturano A, Alfano M, Beccia D, Nevola R, Marfella R, Sardu C, Coppola C, Scarano F, Maggi P, De Lucia Sposito P, Vocciante L, Rescigno C, Sbreglia C, Fraganza F, Parrella R, Romano A, Calabria G, Polverino B, Pagano A, Bologna C, Amitrano M, Esposito V, Coppola N, Maturo N, Adinolfi LE, Chiodini P, Sasso FC; COVOCA Study Group. Impact of chronic liver disease upon admission on COVID-19 in-hospital mortality: findings from COVOCA study. PLoS One 2020; 15: e0243700.
2) Valdenassi L, Franzini M, Ricevuti G, Rinaldi L, Galoforo AC, Tirelli U. Potential mechanisms by which the oxygen-ozone (O2-O3) therapy could contribute to the treatment against the coronavirus COVID-19. Eur Rev Med Pharmacol Sci 2020; 24: 4059-4061.
3) Bosso G, Allegorico E, Pagano A, Porta G, Serra C, Minerva V, Mercurio V, Russo T, Altruda C, Arbo P, De Sio C, Dello Vicario F, Numis FG. Lung ultrasound as diagnostic tool for SARS-CoV-2 infection. Intern Emerg Med 2020; 3: 1-6.
4) Smargiassi A, Soldati G, Borghetti A, Scoppettuolo G, Tamburrini E, Testa AC, Moro F, Natale L, Larici AR, Buonsenso D, Valentini P, Draisci G, Zanfini BA, Pompili M, Scambia G, Lanzone A, Franceschi F, Rapaccini GL, Gasbarrini A, Giorgini P, Richeldi L, Demi L, Inchingolo R. Lung ultrasonography for early management of patients with respiratory symptoms during COVID-19 pandemic. J Ultrasound 2020; 23: 449-456.
5) Soldati G, Smargiassi A, Inchingolo R, Sher S, Nenna R, Valente S, Inchingolo CD, Corbo GM. Lung ultrasonography may provide an indirect estimation of lung porosity and airspace geometry. Respiration 2014; 88: 458-468.
6) Rinaldi L, Milione S, Fascione MC, Pafundi PC, Altruda C, Di Caterino M, Monaco L, Reginelli A, Perrotta F, Porta G, Venafro M, Acierno C, Mastrocinque D, Giordano M, Bianco A, Sasso FC, Adinolfi LE. Relevance of lung ultrasound in the diagnostic algorithm of respiratory diseases in a real-life setting: a multicentre prospective study. Respirology 2020; 25: 535-542.
7) Demi M, Prediletto R, Soldati G, Demi L. Physical mechanisms providing clinical information from ultrasound lung images: hypotheses and early confirmations. IEEE Trans Ultrason Ferroelectr Freq Control 2020; 67: 612-623.
8) Soldati G, Demi M, Smargiassi A, Inchingolo R, Demi L. The role of ultrasound lung artifacts in the diagnosis of respiratory diseases. Expert Rev Respir Med 2019; 13: 163-172.
9) Zieleskiewicz L, Markarian T, Lopez A, Taguet C, Mohammedi N, Boucekine M, Baumstarck K, Besch G, Mathon G, Duclos G, Bouvet L, Michelet P, Allaouchiche B, Chaumoître K, Di Bisceglie M, Leone M; AZUREA Network. Comparative study of lung ultrasound and chest computed tomography scan in the assessment of severity of confirmed COVID-19 pneumonia. Intensive Care Med 2020; 46: 1707-1713.
10) Zhao L, Yu K, Zhao Q, Tian R, Xie H, Xie L, Deng P, Xie G, Bao A, Du J. Lung ultrasound score in evaluating the severity of Coronavirus disease 2019 (COVID-19) pneumonia. Ultrasound Med Biol 2020; 46: 2938-2944.
11) Hussain A, Via G, Melniker L, Goffi A, Tavazzi G, Neri L, Villen T, Hoppmann R, Mojoli F, Noble V, Zieleskiewicz L, Blanco P, Ma IWY, Wahab MA, Alsaawi A, Al Salamah M, Balik M, Barca D, Bendjelid K, Bouhemad B, Bravo-Figueroa P, Breitkreutz R, Calderon J, Connolly J, Copetti R, Corradi F, Dean AJ, Denault A, Govil D, Graci C, Ha YR, Hurtado L, Kameda T, Lanspa M, Laursen CB, Lee F, Liu R, Meineri M, Montorfano M, Nazerian P, Nelson BP, Neskovic AN, Nogue R, Osman A, Pazeli J, Pereira-Junior E, Petrovic T, Pivetta E, Poelaert J, Price S, Prosen G, Rodriguez S, Rola P, Royse C, Chen YT, Wells M, Wong A, Xiaoting W, Zhen W, Arabi Y. Multi-organ point-of-care ultrasound for COVID-19 (PoCUS4COVID): international expert consensus. Crit Care 2020; 24: 702.
12) Lichter Y, Topilsky Y, Taieb P, Banai A, Hochstadt A, Merdler I, Gal Oz A, Vine J, Goren O, Cohen B, Sapir O, Granot Y, Mann T, Friedman S, Angel Y, Adi N, Laufer-Perl M, Ingbir M, Arbel Y, Matot I, Szekely Y. Lung ultrasound predicts clinical course and outcomes in COVID-19 patients. Intensive Care Med 2020; 46: 1873-1883.
13) Mafort TT, Lopes AJ, da Costa CH, da Cal MS, Lopes MC, da Silva BRA, Faria LF, Faria AC, Costa W, Salles REB, de Castro MCS, Rufino R. Changes in lung ultrasound of symptomatic healthcare professionals with COVID-19 pneumonia and their association with clinical findings. J Clin Ultrasound 2020; 48: 515-521.
14) Soldati G, Smargiassi A, Inchingolo R, Buonsenso D, Perrone T, Briganti DF, Perlini S, Torri E, Mariani AA, Mossolani EE, Tursi F, Mento F, Demi L. Proposal for international standardization of the use of lung ultrasound for COVID-19 patients; a simple, quantitative, reproducible method. J Ultrasound Med 2020; 39: 1413-1419.
15) Perrone T, Soldati G, Padovini L, Fiengo A, Lettieri G, Sabatini U, Gori G, Lepore F, Garolfi M, Palumbo I, Inchingolo R, Smargiassi A, Demi L, Mossolani EE, Tursi F, Klersy C, Di Sabatino A. A new lung ultrasound protocol able to predict worsening in patients affected by Severe Acute Respiratory Syndrome Coronavirus 2 Pneumonia. J Ultrasound Med 2020. doi: 10.1002/jum.15548. Epub ahead of print.
16) Yi B, Fen G, Cao D, Cai Y, Qian L, Li W, Wen Z, Sun X. Epidemiological and clinical characteristics of 214 families with COVID-19 in Wuhan, China. Int J Infect Dis 2021; 105: 113-119. doi: 10.1002/jum.15548. Online ahead of print.

17) Song Y, Liu P, Shi XL, Chu YL, Zhang J, Xia J, Gao XZ, Qu T, Wang MY. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. Gut 2020; 69: 1143-1144.

18) Chang R, Elhusseiny KM, Yeh YC, Sun WZ. COVID-19 ICU and mechanical ventilation patient characteristics and outcomes-A systematic review and meta-analysis. PLoS One 2021; 16: e0246318.

19) Pare JR, Camelo I, Mayo KC, Leo MM, Dugas JN, Nelson KP, Baker WE, Shareef F, Mitchell PM, Schechter-Perkins EM. Point-of-care lung ultrasound is more sensitive than chest radiograph for evaluation of COVID-19. West J Emerg Med 2020; 21: 771-778.

20) Hussain A, Mahawar K, Xia Z, Yang W, El-Hasani S. Obesity and mortality of COVID-19. Meta-analysis. Obes Res Clin Pract 2020; 14: 295-300.

21) Cariou B, Pichelin M, Goronflot T, Gonfroy C, Marre M, Raffaitin-Cardin C, Thivolet C, Wargny M, Hadjadj S, Gourdy P; CORONADO investigators. Phenotypic characteristics and prognosis of newly diagnosed diabetes in hospitalized patients with COVID-19: results from the CORONADO study. Diabetes Res Clin Pract 2021; 108695.

22) Yang Y, Cai Z, Zhang J. Hyperglycemia at admission is a strong predictor of mortality and severe/critical complications in COVID-19 patients: a meta-analysis. Biosci Rep 2021; 41: BSR20203584.

23) Sasso FC, Rinaldi L, Lascar N, Marrone A, Pafundi PC, Adinolfi LE, Marfella R. Role of tight glycemic control during acute coronary syndrome on CV outcome in type 2 diabetes. J Diab Res 2018: 3106056.

24) Sasso FC, Pafundi PC, Gelso A, Bono V, Costagliola C, Marfella R, Sardu C, Rinaldi L, Galiero R, Acierno C, De Sio C, Adinolfi LE. Telemedicine for screening diabetic retinopathy: the NO BLIND Italian multicenter study. Diabetes Metab Res Rev 2019; 35: e3113.

25) Sasso FC, Pafundi PC, Marfella R, Calabrò P, Piscione F, Furbatto F, Esposito G, Galiero R, Gragnano F, Rinaldi L, Salvatore T, D'Amico M, Adinolfi LE, Sardu C. Adiponectin and insulin resistance are related to restenosis and overall new PCI in subjects with normal glucose tolerance: the prospective AIRE Study. Cardiovasc Diabetol 2019; 18: 24.

26) Interim Infection Prevention and Control Recommendations for Healthcare Personnel During the Coronavirus Disease 2019 (COVID-19) Pandemic. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html. Updated Feb. 10, 2021.

27) World Health Organization. Novel Coronavirus (2019-nCoV) technical guidance: patient management. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management (Accessed on February 01, 2021).

28) Speidel V, Conen A, Gisler V, Fux CA, Haubitz S. Lung assessment with point-of-care ultrasound in Respiratory Coronavirus Disease (COVID-19): a prospective cohort study. Ultrasound Med Biol 2020; 26: S0301-5629(20)30576-7.

29) Seiler C, Klingberg C, Hårdstedt M. Lung ultrasound for identification of patients requiring invasive mechanical ventilation in COVID-19. J Ultrasound Med 2021; 10.1002/jum.15617. doi: 10.1002/jum.15617. Online ahead of print.

30) Rubio-Gracia J, Giménez-López I, Garcés-Horna V, López-Delgado D, Sierra-Monzón JL, Martínez-Lostao L, Josa-Laorden C, Ruiz-Laiglesia F, Pérez-Calvo JI, Crespo-Aznarez S, García-Lafuente J, Peña Fresneda N, Amores Arriaga B, Gracia-Tello B, Sánchez-Marteles M. Point-of-care lung ultrasound assessment for risk stratification and therapy guiding in COVID-19 patients. A prospective non-interventional study. Eur Respir J 2021; 004283. doi: 10.1183/13993003.04283-2020. Online ahead of print.