

The utility of lung ultrasound in COVID-19 pneumonia in the intensive care unit in real life settings

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ABSTRACT

INTRODUCTION Lung ultrasound is a promising tool for the assessment of patients with respiratory failure in the intensive care unit (ICU). A caveat for the wide implementation of lung ultrasound is its operator-dependence. The aim of our study was to assess the utility of lung ultrasound in critically ill patients with COVID-19 pneumonia in real-life conditions.

METHODS The multi-center Greek RECUP-19 database was used, which prospectively follows patients with COVID-19 pneumonia hospitalized in an ICU. Lung ultrasound was performed as part of the clinical evaluation within 24 hours upon admission. Six regions (upper/lower at the mid-clavicular, mid-axillary and posterior axillary lines) were scanned in each hemithorax, and a score (Lung Ultrasound Score, LUS) was applied (0=normal, 1=multiple discrete B-lines, 2=coalescent B-lines, 3=consolidation). The 28-day mortality, static compliance (Cst), the P:F ratio, and serum CRP were recorded.

RESULTS The study included 29 patients with mean age 67.07 ± 13.69 years. The LUS was not significantly different between survivors (65.5% of patients) and non-survivors (34.5%), (score: 18.58 ± 6.62 vs 22.4 ± 4.20 , $p=0.11$, respectively). LUS was positively correlated with the APACHE-II score ($r=0.49$, $p=0.006$) and negatively correlated with Cst ($r= -0.39$, $p=0.03$). LUS was not correlated with the P:F ratio or CRP ($r= -0.05$, $p=0.78$ and $r=0.19$, $p=0.35$, respectively). Patients with Cst ≥ 40 mL/cmH₂O had a lower score, mainly at the anterior segments of the lungs, compared to Cst < 40 mL/cmH₂O (score: 4.15 ± 2.44 vs 6.75 ± 2.21 , $p=0.005$).

CONCLUSIONS LUS is a useful tool for the evaluation of patients with COVID-19 pneumonia in the ICU, which can be implemented in daily clinical practice.

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INTRODUCTION

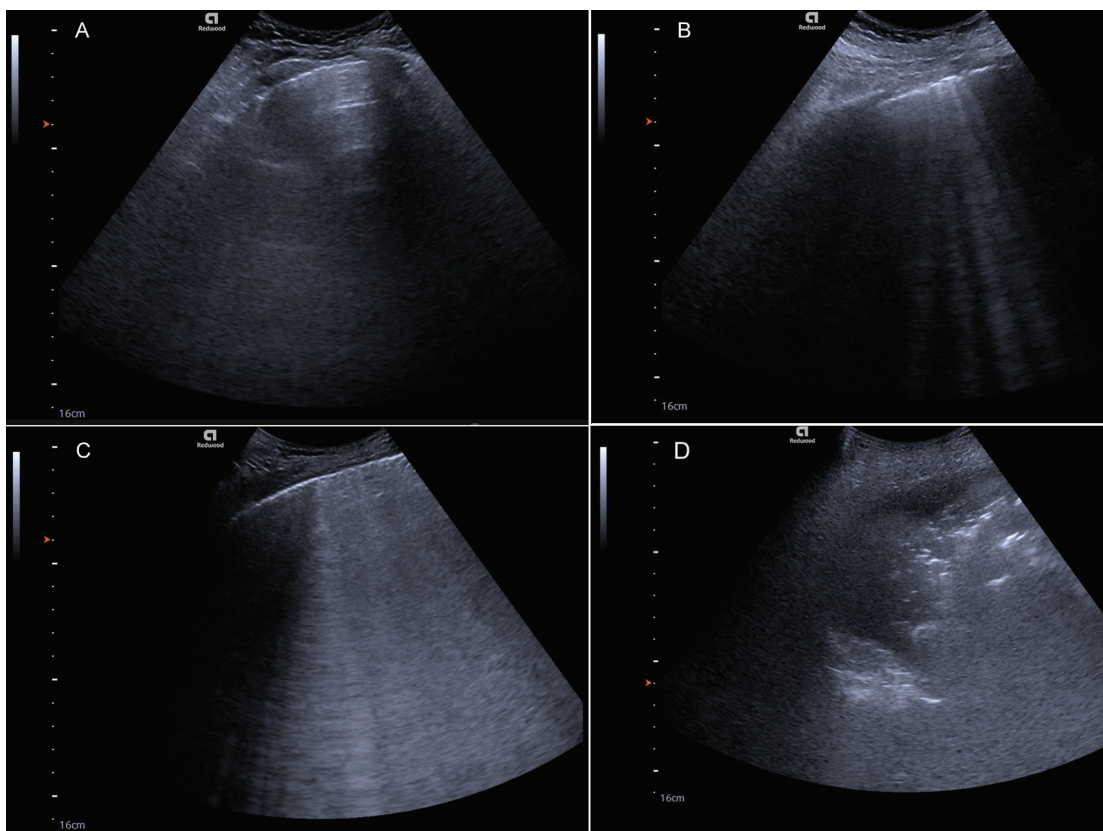
Lung ultrasound has gained increasing importance as an imaging tool in the field of respiratory failure, due to its non-invasiveness, safety, and bedside availability¹. Lung ultrasound enables ARDS diagnosis, with accuracy comparable to chest X-ray interpretation based on guidelines², and the new proposed global definition of ARDS includes the use of ultrasound for the diagnosis of bilateral B-lines and/or consolidation³. Moreover, lung ultrasound outperforms chest X-ray for the differential diagnosis of pulmonary abnormalities in the ICU⁴ and can impact clinical decision making and therapeutic management⁵. Due to these advantages, lung ultrasound has especially been used during the COVID-19 pandemic⁶, allowing the detection of early disease⁷ and follow-up of patients⁸, while minimizing the need of transferring patients to the radiology department and, hence, reducing virus transmission. Moreover, in COVID-19 pneumonia, a lung ultrasound score (LUS) was associated with the disease severity, as assessed by chest CT and clinical

features⁹, the estimation of extravascular lung water¹⁰ and the aeration following prone position¹¹, while it has been shown to enable monitoring of PEEP-induced recruitment in mechanically ventilated patients with ARDS¹².

As a relatively new technology, lung ultrasound has possible pitfalls^{13,14} and a limitation of ultrasound is that it is a technique with high operator dependence¹⁵. This is an important factor for the implementation of ultrasound in 'real-life' clinical practice, especially in the critically ill patient, where clinical instability may require serial monitoring from different attending physicians. Indeed, in previous large observational studies, lung ultrasound was performed by specified trained operators¹⁶.

Thus, the aim of our study was to assess the utility of lung ultrasound performed by different physicians in a multi-center observational study and to correlate lung ultrasound with important outcomes in critically ill patients with COVID-19 pneumonia.

Figure 1. Representative images of lung ultrasound score (LUS)



A semi-quantitative LUS was employed in each examined region¹⁶: A) The presence of A-lines and/or ≤ 2 B-lines was scored as 0 (normal); B) Multiple discrete B-lines as 1; C) Coalescent B-lines as 2; and D) The presence of consolidation as 3.

METHODS

Subjects

Intubated patients due to COVID-19 pneumonia were included in the study. All patients had a positive SARS-COV-2 polymerase chain reaction (PCR) test in bronchial secretions and/or in nasopharyngeal swab. Data were acquired from the multi-center Greek RECUP-19 (Registry of Hellenic ICUs for Pandemic COVID-19) database that prospectively follows patients with COVID-19 pneumonia hospitalized in ICU. The ICU departments of 'Sotiria' Chest Hospital, University Hospital of Heraklion and 'George Papanikolaou' General Hospital of Thessaloniki participated in the study. The study protocol was approved by the Scientific Committee of the participating hospitals. Due to the observational nature of the study, which only collected clinical data from the patients' record, informed consent was waived.

Lung ultrasound protocol

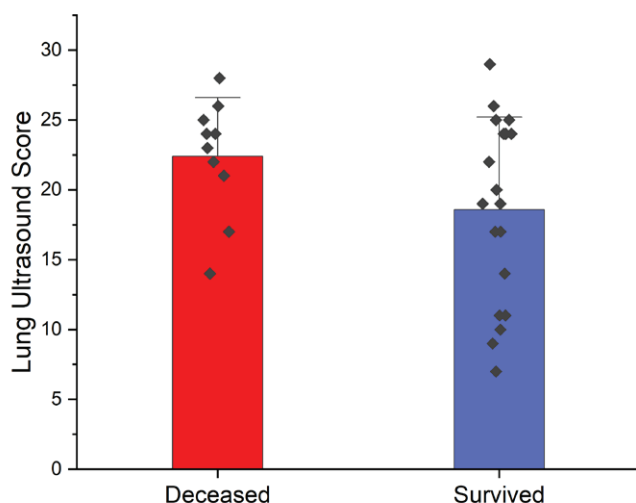
Lung ultrasound was performed as part of the clinical evaluation, within 24 hours upon admission from the attending physician. No examination was performed during or after a prone positioning session. Lung ultrasound was performed on the patient at the supine posture with 30° inclination, using the phased array or the convex (abdominal)

probe, according to Mojoli et al.¹⁷. Each hemithorax was divided into three areas, anterior, lateral, and posterior, defined by the sternum, the anterior, and posterior maxillary lines, respectively. Each region was further divided into an upper and lower zone, creating 6 regions of interest by hemithorax. Lung ultrasound clips were stored for further quantification. Lung ultrasound patterns during a complete respiratory cycle were identified and scored using a semi-quantitative scale, based on the worst identified pattern¹², as follows: 0 = A lines and/or ≤ 2 B-lines (normal), 1 = multiple discrete B lines (moderate loss of aeration), 2 = multiple coalescent B lines (severe loss of aeration), 3 = consolidation (complete loss of aeration). The scores from each region were summed creating a final lung ultrasound score (LUS) ranging from 0 to 36^{12,16,17}. To avoid overestimation, a score of 3 was only given when consolidation was the dominant ultrasound image¹⁷.

Statistical analysis

Data are presented as mean \pm standard deviation. Normality of our data was assessed using the Kolmogorov-Smirnov test. Comparisons between two groups were performed with Student's t-test, and correlations between variables were assessed with the Pearson r correlation coefficient. A $p < 0.05$ was used to denote statistical significance.

Figure 2. Lung ultrasound score upon admission of survivors and non-survivors



There was no difference in LUS upon admission between COVID-19 patients that survived and non-survivors. Data are presented as mean \pm SD. * $p < 0.05$. LUS: lung ultrasound score.

RESULTS

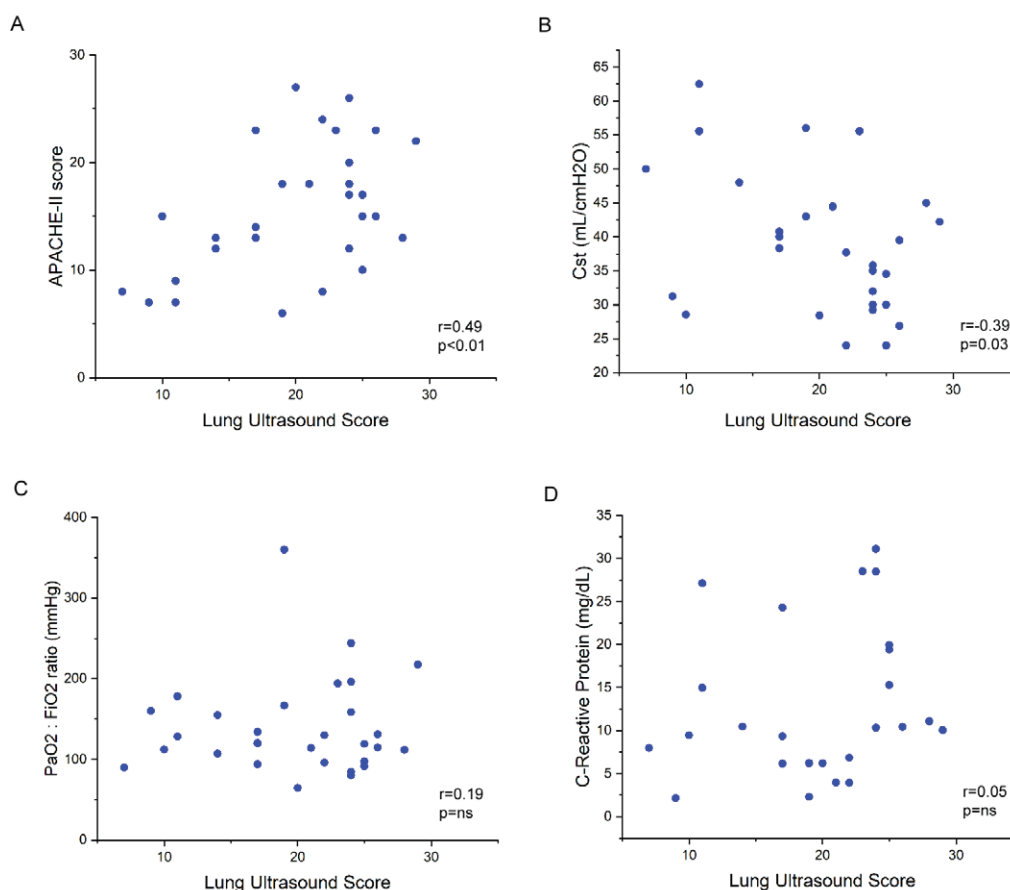
Subjects

Our study included 29 patients with severe COVID-19 pneumonia under mechanical ventilation, with a mean age of 67.07 ± 13.69 years. The APACHE-II mean score upon admission was 15.62 ± 6.08 . Baseline characteristics, including parameters of the mechanical ventilation settings, are presented in Table 1. Mean LUS was 19.83 ± 6.01 . From 348 regions scanned (29 patients \times 12 regions), 8.05% ($n=28$) were scored as 0, 26.15% ($n=91$) were scored as 1, 51.72% ($n=180$) were scored as 2, and 8.05% ($n=28$) were scored as 3. Thus, the presence of multiple B-lines (either discrete or coalescent) was the most frequent finding in our cohort, with 12 patients (41.38%) having at least 1 region scored as 3, i.e. consolidation pattern.

The relationship between LUS and mortality

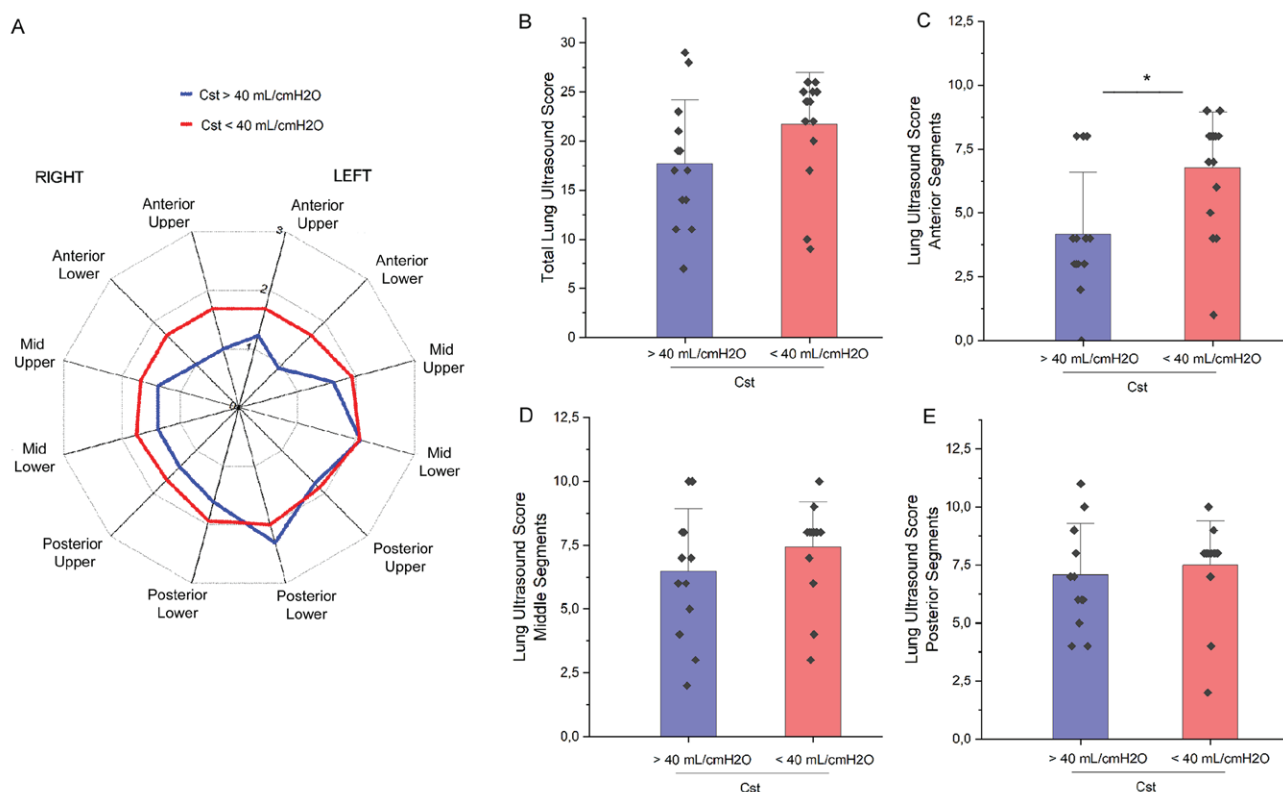
Our cohort presented a 28-day mortality rate of 34.5%. The lung ultrasound score (LUS) upon admission did not differ significantly between survivors and non-survivors (18.58 ± 6.62 vs 22.4 ± 4.20 , $p=0.11$) (Figure 2).

Figure 3. Correlation of LUS upon admission with physiological and clinical characteristics of patients with COVID-19 pneumonia



LUS had a significant moderate correlation with APACHE-II score (A) and a negative correlation with static compliance (Cst) (B). In contrast, neither oxygenation (P:F ratio) (C), nor systemic inflammation (CRP) (D), correlated with LUS. r : Pearson's correlation coefficient. * $p < 0.05$. LUS: lung ultrasound score. APACHE-II: Acute physiology and chronic health evaluation score-II. P:F: PaO₂/FiO₂. CRP: c-Reactive Protein.

Figure 4. Differential LUS per anatomical region and relation to static compliance of the respiratory system



A) Spider diagram depicting the differential LUS per anatomic region in each hemithorax. Note that anterior regions show greater score in patients with Cst <40 mL/cmH2O. Although the difference in total LUS failed to reach statistical significance ($p=0.07$) (B), patients with static compliance lower than 40 cmH2O had significantly higher score in the anterior segments (C) compared to patients with less impaired lung mechanics, whereas no difference was noted for the middle (D) and posterior (E) segments. Data are presented as mean \pm SD. * $p<0.05$.

The correlation of LUS with physiological parameters upon admission

As shown in Figure 3, the LUS upon ICU admission has a significant moderate correlation with APACHE-II score ($r=0.49$, $p=0.006$) and a significant negative moderate correlation with the static compliance of the respiratory system ($r= -0.39$, $p=0.03$). In contrast, no correlation was found with systemic inflammation, as estimated by the c-reactive protein (CRP) ($r=0.19$, $p=0.35$) or with the oxygenation, as estimated by the P:F ratio ($r=0.05$, $p=0.78$).

Estimation of spatial differences in LUS and relationship with respiratory system static compliance

A separate analysis was performed using the cut-off value of 40 mL/cmH2O for static lung compliance, as this has been previously suggested to define severe alteration in lung mechanics¹⁸. As shown in Figure 4, patients with preserved/mildly deranged static lung compliance (Cst \geq 40 mL/cmH2O) had a differential lung ultrasound score per anatomical region, compared to patients with Cst <40 mL/cmH2O. In details, mildly deranged lung mechanics were

Table 1. Physiological characteristics of patients upon admission

Characteristics	Mean \pm SD
Age (years)	67.07 \pm 13.69
Lung ultrasound score (LUS)	19.83 \pm 6.01
APACHE-II score	15.62 \pm 6.08
PaO2 (mmHg)	91.3 \pm 30.9
FiO2	68.8 \pm 16.2
P:F ratio	139.70 \pm 60.51
PaCO2 (mmHg)	44.6 \pm 6.4
pH	7.34 \pm 0.05
Pplat (cmH2O)	24.3 \pm 3.4
PEEPtot (cmH2O)	12.6 \pm 3.6
Driving pressure (cmH2O)	11.6 \pm 2.4
Static compliance (Cst, mL/cmH2O)	39.19 \pm 10.35
C-reactive protein (CRP, mg/dL)	13.0 \pm 8.9

associated with reduced LUS in the anterior segments of the lung, compared to LUS in anterior segments of patients with reduced Cst (4.15 ± 2.44 vs 6.75 ± 2.20 , $p=0.006$), whereas no difference was observed for the posterior segments ($p=0.58$).

DISCUSSION

The main findings of our study are that lung ultrasound upon admission does not predict survival in critically ill patients with COVID-19 pneumonia. However, significant correlations with the APACHE-II score and the mechanical properties of the respiratory system are noted. Moreover, reduced static compliance is associated with higher lung ultrasound score in the anterior segments, compared to preserved static compliance.

The lack of a difference of LUS between survivors versus non-survivors in our study contrasts with a previous study, where lung ultrasound upon hospital admission was a strong predictor of mortality in COVID-19 patients¹⁶. However, this study included patients across all disease stages, whereas in our study we included only critically ill patients in the ICU. Mortality in critically ill COVID-19 patients is shown to be multifactorial, with multiorgan dysfunction syndrome related to both COVID-19 or secondary infections being the most common cause of death in the ICU¹⁹, whereas a minority of patients die from refractory hypoxemia. We also acknowledge that a limitation of our study is the small number of patients that may reduce the power of the study to detect a significant correlation to mortality. Indeed, given the moderate correlation of LUS with the APACHE-II score, it is possible that a significant difference with mortality would be detected, given that a previous retrospective study found that the APACHE-II score upon admission was significantly different between survivors versus non-survivors in COVID-19 pneumonia in the ICU²⁰. Therefore, survival of COVID-19 critically ill patients is dependent on many factors and admission LUS could potentially be among them but not the only one.

An interesting finding of our study is the correlation of lung mechanics with LUS in critically ill patients. This may be of additional value in groups of patients, in whom assessment of the mechanical properties is challenging, such as patients on non-invasive mechanical ventilation or patients on partial support ventilation. Identifying low compliance is, however, essential, since it allows the monitoring of critically ill patients and may unmask high respiratory drive²¹ and increased work of breathing, which may necessitate invasive mechanical ventilation or lead to lung and diaphragm injurious ventilatory settings²². Furthermore, the positive correlation between respiratory system mechanics and LUS can be useful in predicting the responders to recruitment maneuvers. According to the most recently published ESICM guidelines for acute respiratory distress syndrome (ARDS)²³, there is a strong recommendation against the routine use of high-pressure

recruitment maneuvers in ARDS patients and lung ultrasound could be valuable in recognizing the patients that will benefit for these strategies and enable a 'precision medicine' approach.

Despite the correlation of lung ultrasound with lung mechanics, it is of interest to notice the lack of any correlation with oxygenation. Although the reason for this cannot be addressed by our study, some assumptions can be made. Indeed, the contribution of vascular abnormalities to ventilation/perfusion mismatches, which have been found in COVID-19 patients²⁴, would not be identified by lung ultrasound. Moreover, the presence of overdistension and dead space would not contribute to lung ultrasound score¹², although it significantly impacts gas exchange and oxygenation in mechanically ventilated patients²⁵. Our observation that LUS is correlated with the compliance of the respiratory system and not with oxygenation, is in accordance with the mentioned dissociation between compliance and oxygenation in ARDS patients due to COVID-19²⁶. Furthermore, the same dissociation was observed retrospectively in ARDS before the COVID-19 pandemic²⁷ and not only in the early phase of ARDS, but also in persistent ARDS²⁸. The lack of LUS correlation with CRP, a systemic marker of inflammation, contrasts with previous studies where LUS was positively associated with CRP levels^{29,30}. However, these studies were performed in patients admitted to the hospital ward, whereas in our study critically ill patients were included upon ICU admission, therefore CRP levels could be affected by prior in-hospital treatments.

Our results also raise the intriguing possibility that lung ultrasound may be used to assess focal distribution of lung injury with interactions with lung mechanics. As shown, severe derangement of static lung compliance was associated with increased LUS in the anterior segments of the lung. Thus, a spatial analysis of lung ultrasound, together with the overall score, may further assist in identifying patients with severely impaired lung physiology. This is a further advantage of ultrasound, since focal distribution is currently assessed by CT imaging, that is associated with radiation exposure and a need for transportation or by technologies such as the electrical impedance tomography^{31,32}, which, although helpful, is not widely available in clinical practice. Previously, spatial analysis of lung ultrasound and a reduction of lung ultrasound score in dorsal regions after prone position was able to identify patients with a positive response to prone position¹¹.

CONCLUSIONS

Lung ultrasound performed under 'real-life' conditions adds valuable information in the clinical evaluation of critically ill patients with COVID-19 pneumonia in the ICU, although it is not associated with overall 28-day mortality. Our data support the implementation of lung ultrasound in clinical practice within the ICU, even (or especially) under crises,

like the recent COVID-19 pandemic. Strategies to increase the awareness of the utility of lung ultrasound and widen its current use, through structured educational activities should be undertaken.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for disclosure of Potential Conflicts of Interest and none was reported.

FUNDING

There was no source of funding for this research.

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was obtained from the Scientific Committees of the participating hospitals: 'Sotiria' Chest Hospital, University Hospital of Heraklion, and 'George Papanikolaou' General Hospital of Thessaloniki (Approval numbers: 11621, 13421 and 42/10; Dates: 30 April 2020, 16 December 2020, and 20 May 2020). Due to the observational nature of the study which only collected clinical data from the patients' records, informed consent was waived.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

DISCLAIMER

A. Koutsoukou reports that she is an Editorial Board Member of Pneumon. She had no involvement in the peer-review or acceptance of this article, and had no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to a handling editor of the journal.

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