Diagnostic value of lung ultrasonographic parameters in predicting outcomes of coronavirus disease 2019 (COVID-19) in oxygen-dependent patients requiring intensive care unit treatment

K. V. Kalashnyk, M. Yu. Kolesnyk, O. V. Riabokon, V. V. Cherkaskiy

Zaporizhzhia State Medical and Pharmaceutical University


Materials and methods. We examined 105 patients with COVID-19 who needed supplemental oxygen and were treated in the Department of Anesthesiology and Intensive Care. The age of patients ranged between 39 and 80 years. 63 patients were male and 42 – female. To determine the diagnostic value of lung ultrasound parameters in predicting the severe course of COVID-19 in oxygen-dependent patients, they were divided into groups: Group I – recovered patients (n = 39); Group II – patients with a fatal outcome (n = 66). In all the patients, the diagnosis of COVID-19 was confirmed by RNA-SARS-CoV-2 detection in nasopharyngeal swab specimens. The patients were examined and treated according to the Protocol of the Ministry of Health of Ukraine. The lung ultrasound protocol used in the study included 14 lung examination zones and a score of lung tissue infiltration degree from 0 to 3 points. Statistical processing of the data was performed with Statistica for Windows 13 (StatSoft Inc., No. JPZ04132130AFCN10-J).

Results. In oxygen-dependent patients with severe COVID-19 and a fatal outcome, infiltrative changes in the lung parenchyma were more severe based on the lung ultrasound total score both at the time of admission (p < 0.01) and after 5 days of treatment (p < 0.01). The cutoff score of ≥19 at the time of hospitalization (AUC = 0.743, p < 0.01; sensitivity – 76.9 %, specificity – 68.2 %) and ≥17 after 5 days of treatment (AUC = 0.709, p < 0.01; sensitivity – 71.4 %, specificity – 92.1 %) had a prognostic value for assessing the risk of death in oxygen-dependent patients with severe COVID-19. A lung ultrasound score >19 at the time of admission increased the risk of death by 2.96 times (RR = 2.96, 95 % CI 1.43–2.87, p < 0.001). Lung ultrasound found pleural effusion only in oxygen-dependent COVID-19 patients who died. In the treatment dynamics after 5 days, the rate of pleural effusion detection in this group of patients was three times increased (from 9.1 % to 27.3 %, p < 0.01).

Conclusions. The study has revealed the diagnostic value of lung ultrasound parameters in predicting outcomes of COVID-19 in oxygen-dependent patients requiring intensive care unit treatment. Cutoffs of the total score characterizing the degree of lung tissue infiltration have been determined, that allowing to assert a high probability for a lethal outcome of the disease.

Keywords: coronavirus disease, COVID-19, lung, diagnostic ultrasound, diagnosis, treatment, prognosis.
Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, the world has needed a fast and safe method for visualizing lung damage. Already in mid-2020, the World Health Organization (WHO) provided recommendations on the choice of imaging methods to determine lung damage in COVID-19 [1], in which lung ultrasound (LUS) was recommended as an alternative method of examination, especially for sensitive populations (pregnant women, children, etc.) and patients with severe disease admitted to intensive care units (ICU).

The history of LUS in humans dates back to 1961, when a group of researchers provided the first characteristics of LUS [2]. The first artifacts, currently found, were named “A-lines” [3]. Subsequently, in 1967, two independent groups of researchers described LUS patterns that were characteristic of patients with pulmonary thromboembolism [4] and pleural effusion [5]. Studies on LUS diagnostic capabilities continued, and the “comet tail artifact” was described in 1982 [6], which later got the name of “B-line” [3]. In 1997, D. Lichtenstein et al. confirmed the importance of this artifact as a marker of alveolar-interstitial lung parenchymal edema in various pathological conditions [7].

In 2012, the first consensus [3] on the LUS technology was formed, it was updated in 2022 and recommendations for the interpretation of LUS findings were developed [8]. In a systematic review [9] of publications on LUS, researchers presented a large number of studies. They noted the availability of general recommendations on the technique, but there was no general protocol for LUS. Thus, the number of zones on the chest that are recommended by different scientists to be examined ranges from 8 to 14 [10,11,12,13]. Approaches to quantification of ultrasound findings also vary. They are evaluated both on a scale of 0 to 3 points [12,13,14] and on a scale of 0 to 4 points [15].

LUS gained clinical importance during the pandemic of new COVID-19. This was due to a sharp increase in demand for visualization of changes in the lung parenchyma and detection of pneumonia signs. However, with such a burden on the medical system, it was impossible to perform computed tomography or chest radiography on all patients in time. Therefore, the WHO [1] published a recommendation on the use of LUS. This was driven by a low cost, a possibility of performing examinations at the patient’s bedside, the so-called “point-of-care” principle [16], and the absence of radiation exposure, which allowed for multiple examinations. Today it is clear that oxygen-dependent patients with COVID-19 cannot always be transported for chest computed tomography. The 2022 consensus [8], after reviewing publications on the clinical characteristics of ICU patients, also recommended LUS for routine use in critically ill patients.

In 2020, a group of researchers [13] made a proposal to the community of scientists to unify the system for evaluating LUS findings. It was proposed to use 14 zones of parenchymal lesions with scores from 0 to 3. According to the authors, this approach to LUS was to improve the quality of the data obtained, examine patients more fully, and allow for future analysis of the results and the development of forthcoming recommendations [13].

Lung ultrasonography allows assessing the presence of interstitial pulmonary edema in various pathologies, and in combination with other laboratory data, can provide much more useful information for clinicians [17,18]. Therefore, in our opinion, it is advisable to clarify the diagnostic assessment of the lung damage degree in COVID-19 patients, primarily in those with severe disease and oxygen dependence requiring ICU treatment.

**Aim**

The aim of the study – to define the diagnostic value of lung ultrasound parameters in predicting COVID-19 outcomes in oxygen-dependent patients requiring intensive care unit treatment.

**Material and methods**

The study included 105 patients with COVID-19 who needed supplemental oxygen and were treated in the ICU of the Municipal Non-Profit Enterprise “Regional Infectious Diseases Clinical Hospital” of Zaporizhzhia Regional Council. The age of patients ranged between 39 and 80 years, with a median age of 66.0 [54.0; 71.5] years. There were 63 men and 42 women.

To determine the diagnostic value of LUS parameters in predicting the severe course of COVID-19 in oxygen-dependent patients, they were divided into groups: Group I – recovered patients (n = 39); Group II – patients with a fatal outcome (n = 66). In all the patients, the diagnosis of COVID-19 was confirmed by RNA-SARS-CoV-2 detection in nasopharyngeal swab specimens by polymerase chain reaction. The patients were examined and treated in accordance with the Order of the Ministry of Health of Ukraine No. 722 dated 28.03.2020 “Organization of Medical Care for Patients with Coronavirus Disease (COVID-19)” (as amended by the Order of the Ministry of Health of Ukraine No. 2122 dated 17.09.2020 “On Amendments to the Standards of Medical Care “Coronavirus Disease (COVID-19)”; Order of the Ministry of Health of Ukraine No. 10 dated 07.01.2021 “On Approval of Amendments to the Medical Care Standards “Coronavirus Disease (COVID-19)”; Order of the Ministry of Health of Ukraine No. 638 dated 06.04.2021 “On Amendments to the Protocol “ Provision of Medical Care for the Treatment of Coronavirus Disease (COVID-19)”.

LUS was performed at the time of ICU admission and in the dynamics after 5 days.

The LUS protocol used in this study included 14 lung examination zones (Fig. 1) and a score from 0 to 3 based on the following sonographic findings [13]:

- 0 points – normal lung parenchyma with A-lines (or less than 3 B-lines) and no other artefacts;
- 1 point – signs of interstitial parenchymal edema (3 or more B-lines, “white lung” phenomenon, unchanged pleural line);
– 2 points – signs of superficial consolidation (3 or more B-lines, “white lung” phenomenon, pleural line abnormalities);
– 3 points – signs of large parenchymal consolidations (complete distortion of lung tissue architecture; so-called “air-bronchogram” – a phenomenon with significant parenchymal consolidation, i.e., visibility of small airways.

The scores in all the zones were added up and a total score of examinations was presented ranging from 0 to 42 points.

An expert-class ultrasound machine GE LOGIQ P9 (USA) with a modified Abdomen preset was used in the study to better visualize artefacts from the pleura and lung parenchyma. The settings were changed as follows:
1. A convection probe was used with a frequency of 3–5 MHz;
2. The focus point was set at a depth of 5–7 cm at or below the level of the pleura line;
3. The initial depth of the examination – 14 cm;
4. Multifocus – turned off;
5. Artefact reduction settings – turned off;
6. Signal amplification was adjusted to a minimal level for better visualization of artefacts.

The data obtained during the study were statistically processed using the formed patient database in the program Statistica for Windows 13 (StatSoft Inc., No. JPZ8041382130ARCN10-J). The following statistical methods were used to analyze the results: differences between quantitative indicators in the independent groups were determined by the Mann-Whitney test, and in the dependent groups – by the Wilcoxon test. Differences in qualitative values were determined using the $\chi^2$ test. ROC analysis (15-day trial version of MedCalc Version 22.016 x64) was used to find the cut-off points for the sum of scores. The relative risk level (Relative risk-RR) was also calculated in MedCalc Version 22.016 x64.

Results

According to the study results, it has been found that hospitalization of oxygen-dependent patients with severe COVID-19 to the ICU occurred on the second week of the disease, namely, in Group I patients – on day 9.0 [7.0; 11.0] and in Group II patients – on day 8.0 [6.0; 11.0]. At the same time, there was no statistically significant difference in the

Fig. 1. Standardized areas of lung ultrasound in patients with COVID-19 [13].
hospitalization time of patients between the study groups (p > 0.05). Oxygen saturation when breathing air on admission to the ICU in Group II patients had a clear tendency to a lower level than that in Group I patients and was 79.0 [77.5; 84.5] % against 84.0 [80.0; 88.0] %, respectively (p > 0.05). The mean age of patients did not differ statistically (p > 0.05) between the study groups.

At the time of hospitalization, LUS in all the patients revealed signs of lung parenchymal infiltration, ranging from 0 to 3 points, and were most pronounced in the lower basal pulmonary segments. In Fig. 2, we provide examples of the lung parenchyma infiltration degree in points based on our own observations.

In the next part of our work, we quantified the severity of pulmonary infiltrative changes by the sum of scores obtained. It has been revealed that at the time of admission to the ICU of oxygen-dependent patients with COVID-19, this parameter was statistically significantly higher in Group II patients who died compared with Group I patients who recovered (p < 0.0001). Quantitative assessment of the total scores in the dynamics after 5 days has enabled to determine a certain relationship between an increase in the severity of changes and an unfavorable outcome of the disease in the future.

So, after 5 days of complex treatment, in Group II patients, there was a further increase in the severity of pulmonary infiltrative changes, which was confirmed by a statistically significant increase in the median score according to LUS (p < 0.05), indicating a worsening of the interstitial edema severity in the lung parenchyma. In contrast to Group II patients, Group I patients, who recovered, showed stabilization of the pulmonary infiltration severity, which was confirmed by the absence of statistically significant changes in this parameter in the dynamics after 5 days (p = 0.47) (Table 1).
Based on the data obtained, in further calculations, we were looking to determine the threshold value of the total scores to assess the diagnostic value of this parameter in predicting the risk of developing a lethal outcome of COVID-19. To that end, we have performed a ROC analysis stating that the score characterizing the pulmonary infiltration severity ≥19 (AUC = 0.753, p < 0.01) indicated a high risk of developing a lethal outcome in the future (sensitivity – 76.9 %, specificity – 68.2 %) in oxygen-dependent patients on admission to the ICU (Fig. 3A).

We also calculated the threshold level of the total scores characterizing the severity of pulmonary tissue infiltration when examining patients in the dynamics after 5 days of complex treatment in the ICU. It has been found that this indicator ≥17 during the follow-up period indicated a risk of death (AUC = 0.799, p < 0.01) (sensitivity – 71.4 %, specificity – 92.1 %) (Fig. 3B). Death from COVID-19 in Group II patients was recorded on day 26.5 [18.5; 29.0] of the disease.

The level of sensitivity did not change significantly in both calculations, unlike the level of specificity. However, it should be noted that at the time of LUS in the dynamics of the 5-day follow-up, the condition of Group II patients was

### Table 1. Comparison of lung ultrasonography results in oxygen-dependent patients with severe COVID-19 in the dynamics depending on the disease outcome

<table>
<thead>
<tr>
<th>Parameter, units of measurement</th>
<th>At the time of hospitalization</th>
<th>After 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I, n = 39</td>
<td>Group II, n = 66</td>
</tr>
<tr>
<td>Sum of scores, Me [Q25; Q75]</td>
<td>16.0 [16.0; 19.0]</td>
<td>22.0 [18.0; 26.0]</td>
</tr>
<tr>
<td>Pleural effusion, absolute (%)</td>
<td>–</td>
<td>6 (9.1 %)</td>
</tr>
<tr>
<td>Spontaneous pneumothorax, absolute (%)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

1: significant differences in comparison to Group I patients at the time of hospitalization (p < 0.01);
2: significant differences in comparison to the corresponding group of patients at the time of hospitalization (p < 0.05).

### Table 2. Risk assessment in oxygen-dependent patients with COVID-19 according to LUS at the time of ICU admission

<table>
<thead>
<tr>
<th>Point</th>
<th>Group I, n = 39</th>
<th>Group II, n = 66</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤19 points</td>
<td>30</td>
<td>21</td>
<td>RR = 2.96, 95 % CI 1.43–2.87, p &lt; 0.001</td>
</tr>
<tr>
<td>&gt;20 points</td>
<td>9</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. ROC analysis showing the diagnostic value of the total scores characterizing the pulmonary infiltration severity according to LUS in predicting the course of COVID-19 in oxygen-dependent patients on admission to the ICU (A) and in the dynamics of the 5-day follow-up (B).

Fig. 4. Schematic representation of pleural effusion in oxygen-dependent patients infected with COVID-19 (own observation).
objectively more severe due to the progression of acute respiratory distress syndrome, in oxygen-dependent of whom, the need for a statistically significantly higher oxygen flow to maintain oxygen saturation above 95 % was confirmed, as compared to Group I patients. So, the rate of oxygen flow in Group II patients was 30.0 [20.0; 40.0] l/min versus 15.0 [10.0; 25.0] l/min in Group I patients (p = 0.002). Therefore, it is of importance to understand how much the risk of death increases when the score exceeds ≥19. For this purpose, we calculated the level of relative risk (RR) determining that the total score exceeding >19 on admission of oxygen-dependent patients with COVID-19 to the ICU increased the relative risk of death by 2.96 times (95 % CI 1.43–2.87) (Table 2).

Among other LUS findings in oxygen-dependent patients with COVID-19 treated in the ICU, the complex treatment follow-up found signs of pleural effusion and spontaneous pneumothorax only in patients with further adverse disease course.

Ultrasonographic signs of pleural effusion were detected in 6 (9.1 %) Group II patients upon admission to the ICU, and the incidence of pleural effusion detection was 3 times higher (27.3 % vs. 9.1 %, χ² = 7.33, p < 0.01) in the 5-day follow-up (Table 1). Fig. 4 presents our own ultrasound detection of pleural effusion signs in the pleural cavity of an oxygen-dependent patient with critical course of COVID-19.

Only 3 (4.5 %) Group II patients developed spontaneous pneumothorax in the dynamics with subsequent fatal outcome (Table 1).

Discussion

Based on our study results, oxygen-dependent COVID-19 patients with unfavorable outcome of the disease had significantly higher degrees of pulmonary tissue infiltration at the time of ICU admission compared to patients who recovered. LUS has revealed not only severe bilateral interstitial edema of the lung parenchyma, but also superficial and large consolidations in Group II patients who died. It should be noted that in addition to these more clear infiltrative changes in the lungs, pleural effusion was detected only in Group II patients at the moment of hospitalization. The data obtained are comparable to the results of other researchers.

So, a study [19] conducted with the enrolment of 130 COVID-19 patients has determined that total scores on admission in patients who died from the disease was also significantly higher compared to those in survivors. Even without considering 12 examination zones used by researchers, this suggests that high values of total LUS scores are prognostically unfavorable. In 2022, researchers also obtained similar data [20] through a large systematic analysis showing an average score of 22.52 in patients admitted to the ICU by also scanning 12 zones. Studies with this number of examination zones were conducted since that is the number used by many publications of that time. However, according to other authors [13], it makes sense to expand LUS examinations up to 14 zones to obtain a more complete picture of the lungs, especially on the posterior chest surface.

Based on our findings, the presence of pleural effusion (unilateral or bilateral) on admission to the ICU was detected only among Group II patients. The fact of such detection has been seen in other studies. For example, a group of researchers [21] examined 280 patients with COVID-19 and divided them into mild, moderate, and severe cases. Pleural effusion was observed exclusively among patients with the severe disease course (5 out of 57, 8.8 %). According to a meta-analysis [20], pleural effusion was detected in patients treated in the ICU with an incidence of 25 %. It should also be noted that in our study, the incidence of pleural effusion was 3 times higher in oxygen-dependent patients with COVID-19 who died, meaning that the presence of pleural effusion (unilateral or bilateral) worsened the prognosis of the disease.

We performed LUS in oxygen-dependent patients with COVID-19 in the ICU in the dynamics of complex treatment, which made it possible to assess changes in the severity of pulmonary infiltrative changes by the total points for patients with severe course of the disease. As a result, it has been found that in Group I patients, the total scores characterizing the degree of pulmonary tissue infiltration did not increase in the dynamics, unlike those in Group II patients, in whom this indicator was statistically significantly increased after the 5-day follow-up. In other words, we have clearly demonstrated that due to the usability of LUS, it was possible not only to assess the state of the lung parenchyma in the dynamics, but also to predict probable treatment outcomes. In the literature available to us today, we have not found studies on the calculation of prognostic values of the pulmonary parenchymal infiltration severity, expressed in quantitative parameters, namely the total points, in the treatment dynamics in the ICU. We believe that this method is informative in the dynamics of follow-up for this category of patients and requires further improvement.

The ROC analysis resulted in a cut-off value of ≥19 points, which allowed to consider oxygen-dependent patients with COVID-19 at high risk of death at the time of ICU admission. Such calculations were carried out by other authors, namely [20], where the cut-off value was a score of 17 points. That is, patients who exceeded this score had an unfavorable outcome of treatment in the ICU. It should be emphasized that the authors calculated this cut-off point for a protocol of 12 examination zones. In other studies, the results were also similar: the total of 18 points [19], 21 points [22], 22 points [23], 15 points (but the protocol included 8 examination areas) [24]. In all the above literature, there was a statistically significant difference in the score between the groups of patients who survived or died.

After receiving data on the cut-off point, we calculated the relative risk of death in oxygen-dependent patients with severe COVID-19 when the total of 19 points (95 % CI 1.43–2.87) was exceeded by the results of LUS at the time of ICU admission. It has been found that in this case, the risk of death was increased almost 3-fold. Other researchers have found a similar pattern, namely the authors [25] examined patients in the ICU also according to a 14-zone LUS protocol and determined a cut-off value that was the total points > 24. The authors have calculated the relative risk when exceeding this value, namely a 6-fold increase in the risk of death (95 % CI 1.29–24.8). A study [19] has demonstrated a 2.6-fold increase in the risk of death in patients with severe COVID-19 when the score exceeded 18 (95 % CI 1.14–6.30).
Conclusions

1. In oxygen-dependent patients with severe COVID-19 who require treatment in the ICU followed by a fatal outcome, the severity of infiltrative changes in the lung parenchyma is higher in terms of the total lung ultrasound scores both at the time of admission to the ICU (p < 0.01) and after 5 days of treatment (p < 0.01).

2. The prognostic value for assessing the risk of death in oxygen-dependent patients with severe COVID-19 requiring treatment in the ICU is an increase in the total score threshold ≥19 at the time of hospitalization (AUC = 0.753, p < 0.01; sensitivity = 76.3 %, specificity = 68.2 %) and ≥17 after 5 days of treatment (AUC = 0.799, p < 0.01; sensitivity = 71.4 %, specificity = 92.1 %).

3. Exceeding a lung ultrasound score of >19 at the time of admission to the ICU increases the risk of death by 2.96 times (RR = 2.96, 95 % CI 1.43–2.87, p < 0.001) in oxygen-dependent patients with severe COVID-19.

4. The presence of pleural effusion (unilateral or bilateral) in lung ultrasound images in oxygen-dependent patients with severe COVID-19 requiring treatment in the ICU is detected only in those with a fatal outcome. In the dynamics after 5 days of treatment, the incidence of pleural effusion detection in this group of patients is increased 3-fold (from 9.1 % to 27.3 %, χ2 = 0.01, p < 0.01) in oxygen-dependent patients with severe COVID-19.

Prospects for further research. In our view, the identified informativeness of quantifying the degree of infiltrative changes in the lung parenchyma for oxygen-dependent COVID-19 patients with severe disease to predict the risk of death indicates the prospects of using LUS data in assessing the treatment effectiveness for patients in the ICU setting.

Conflicts of interest: authors have no conflict of interest to declare.

Information about the authors:
Kalashnyk K. V., MD, PhD, Associate Professor of the Department of Infectious Diseases, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine. ORCID ID: 0000-0002-4532-8953
Kolesnyk M. Yu., MD, PhD, ScD, Professor of the Department of Therapy and Cardiology, Educational and Scientific Institute of Postgraduate Education, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine. ORCID ID: 0000-0001-7566-1899
Ribakon D. V., MD, PhD, DSc, Professor, Head of the Department of Infectious Diseases, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine. ORCID ID: 0000-0002-7394-4649
Cherkaskiy V. V., MD, Assistant of the Department of Infectious Diseases, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine. ORCID ID: 0000-0003-2059-8803

References


