Article

COVID-19 in Infants and Children under 2 years – Lung Ultrasound Score Correlated with Biomarkers and Symptoms

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Abstract: It is already well known that infants and children infected with COVID-19 develop mild to moderate forms of the disease, with fever and oropharyngeal congestion being the most common symptoms. Nevertheless, there are cases in which the patients accuse respiratory symptoms. These cases need lung evaluation, which can be done using lung ultrasound (LUS), because it is a non-irradiating and repeatable imaging technique. 19 children with COVID-19 pneumonia were evaluated using LUS. The LUS score (LUSS) for each patient varied between 1 to 8 points from a maximum of 36 points. The arithmetic mean was 4.47 ± 2.36 (S.D), while 95% CI for the Arithmetic mean was 3.33 to 5.61. The lung changes were correlated with their biomarkers, specifically inflammatory markers. The correlation between LUSS and LDH, D-dimers and IL-6 was a strong positive one with r=0.66 (p=0.01, 95% CI 0.147 to 0.896) between the LUSS and LDH level at symptomatic infants and children (with cough present) and r=0.66 (p=0.01, 95% CI 0.140 to 0.895) between LUSS and D-dimers level at symptomatic infants and children (with cough present). The results suggest that LUS could be a good imaging technique that can be used both in initial evaluation of children with respiratory diseases, and, also in their follow-up, correlated with symptoms and biomarkers.

Keywords: lung ultrasound; infants; children; COVID-19; SARS-CoV-2; multisystem inflammatory syndrome

1. Introduction

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Nowadays, thoracic ultrasound technique has become an useful tool in respiratory pathologies' exploration, especially in children, infants and newborns, respecting the ALARA principles [1]. With the advantages of being a non-irradiating and non-invasive method, this technique could replace conventional radiography in detection of subpleural injuries of the lung [1,2]. Ultrasonography is more accessible and repeatable, and can also be used at the patients' bedside, and can be employed for diagnostic, prognosis, and monitoring infants with lung injuries [3,4]. Lovrenski concludes that the most important feature of lung ultrasound (LUS) is that it does not lie – if something can be found by this imaging technique, it is there [1,5].

The SARS-CoV2 infection and COVID-19 pneumonia seem to be suitable for this kind of examination because the lung areas often affected in this pathology are the subpleural and posterior lung fields, that can be optimally explored using this technique [6]. Campagnano et al. concluded that lung ultrasound has a higher sensitivity compared to computer tomography in detection of lesions in the inferior and posterior fields of the lung, in subpleural region where the COVID-19 pneumonia will be often expressed, like an alveolar-interstitial injury [6]. Also, HRCT has proven to be more effective in evaluating severe cases of lung injuries, while children infected by SARS-CoV2 mostly have mild forms of the disease [3,7].

The manifestations of neonates and children with SARS-CoV2 infection mainly include fever, lack of appetite, respiratory symptoms (such as cough and pharyngitis), diarrhea, and lethargy [4,6]. Studies show that the laboratory findings are non-specific, but most of them include high levels of C-reactive protein, and leukocytes, lymphopenia, and abnormal hepatic probes [4,6,7].

The primary changes that can be found using LUS in evaluating children with SARS-CoV2 include:

- transverse physiologic A-lines, that depict healthy parenchyma,
- intensity reduction of physiological A-lines, up to the disappearance
- isolated vertical B-lines, which translates to interstitial edema;
- conflating vertical B-lines, meaning alveolar edema;
- subpleural/peripheral consolidations;
- irregularities and thickening of the pleura [8,9].

This paper has the purpose of finding the main respiratory changes given by SARS-CoV2 in the infected infants and children under two years, by using LUS. The study also aims to determine a correlation between the lung injuries, and the clinical manifestations and laboratory findings in the infected infants.

2. Materials and Methods

The foundation of this article is the analysis of key symptoms and biomarkers levels of infants and children infected with SARS-CoV2, in correlation with imaging techniques – lung ultrasound in this case. The actual prospective study was performed at Clinical Infectious Diseases II and Infectious Diseases - Intensive Care Unit, wards that have beds for pediatric population, at Clinical Hospital of Infectious Diseases and Pneumophysiology 'Dr. Victor Babes' Timisoara, between November 2021 to the end of October 2022.

Inclusion criteria used in patient selection were as follows:

- Infants with SARS-CoV2 infection that were hospitalized for more than two days;
- Children under 2 years old with SARS-CoV2 infection that were hospitalized for more than two days.

The exclusion criteria were:

- Infants and children with SARS-CoV2 infection that were hospitalized for less than two days;

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- Children over the age of 2 years with SARS-CoV2 infection and COVID-19 pneumonia;
- Infants and children whose owner or legal guardian has not given their consent for data processing.

These criteria listed above are presented in the following scheme – Figure 1.

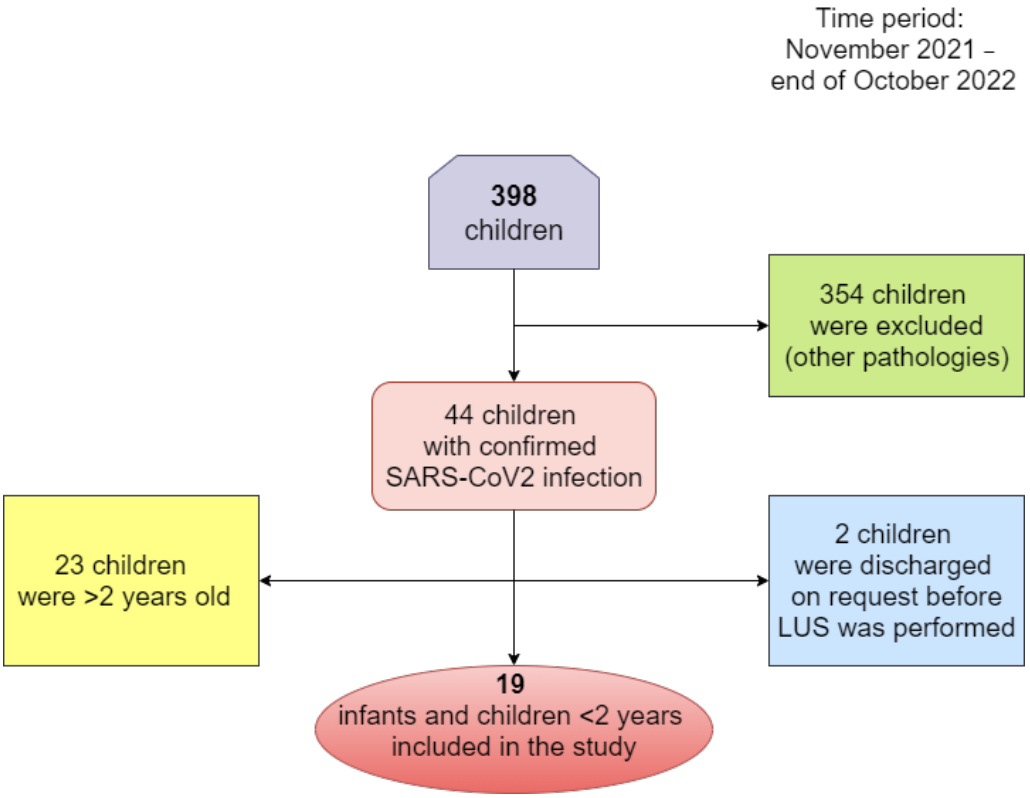

Figure 1. The algorithm of subjects' selection and exclusion criteria

The analysed data was extracted from the hospital's computer program – virtual archive (InfoWorld), stored in a Microsoft Office Excel table, that helps to a better comparison and organization of patient records. The most significant parameters that were considered for the analysis were:

- gender;
- age (months);
- anthropometric measurements (weight of children);
- number of positive PCR tests;
- days of hospitalization/ days of convalescence;
- signs and symptoms of the infection in newborns (psychomotor agitation, asthenic syndrome, fever, cough, rhinorrhea, acute dehydration syndrome, vomiting, diarrhea, nasal obstruction, dysphagia, dysphonia, loss of appetite, dyspnea, oropharyngeal candidiasis, presence of inflammatory lymph nodes, presence of congestive pharynx);
- other associated pathologies;
- biological markers and inflammatory probes (hemoglobin, leukocytes, lymphocytes, neutrophiles, monocytes, thrombocytes, erythrocyte sedimentation rate, procalcitonin, C-reactive protein, ferritin, LDH, hepatic transaminases, bilirubin, D-dimers level, fibrinogen, interleukin-6);
- bacterial and fungal cultures;
- imaging examinations;
- score of lung affection based on ultrasound.

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The lung ultrasound examination was performed in the first days (2nd to 4th day) of hospitalization, in all included cases, conducted by a radiologist with three year-experience in lung ultrasound in newborns, children and adults, verified and analyzed by radiologist with nine years' experience. The examinations were conducted using a portable General Electric Vivid IQ with linear probe 9L-RS [2.4 – 10.0MHz] and convex probe 4C-RS [1.5 – 5.0MHz]. For 6 infants and children was achieved a second look at lung ultrasound, but only the most representative one was included in the actual study from the point of view of suggestive symptomatology.

A 12-area score was accounted for each infant or child admitted to hospital. This score is similar to the one described by Mongodi et al. and used for COVID-19 pneumonia in neonates – Lung UltraSound Score (LUSS) [4,10]. Each area explored was scored between 0 to 3 points, depending on the aspect of artefacts and presence or absence of subpleural consolidation: LUSS = 0 points for normal/physiological A-lines, one or two B-lines per intercostal space; LUSS = 1 points for more than two B-lines (sparse B-lines) per intercostal space with associated pleural abnormalities (irregularities, thickening); LUSS = 2 points for coalescent or confluent B-lines, 'white-lung' aspect or small peripheral consolidation (smaller than 1 cm); LUSS = 3 points for large peripheral consolidation (wider than 1 cm) in association or not with air bronchogram [4,10].

No one of the infants or children were examined by conventional radiography or computer tomography.

All data and analyses have been processed with a licensed version of MedCalc® Statistical Software version 20.026 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022). The central tendency indicators were arithmetic mean and of dispersion – standard deviation (S.D.). The values were reported as mean ± S.D. The relationship between symptoms and lung ultrasound score has been documented through statistical tests, chi-square ($\chi 2$) tests with two variables (bi-directional classification) and cross tabs for better illustration. The difference between the sample means was demonstrated using the independent sample t-tests. Moreover, Pearson's correlation coefficient r between LUSS, biomarkers of inflammation, and symptoms were calculated, based on the degree of correlation: with r near ± 1, the correlation is perfect; strong correlation with r between ± 0.5 to ± 1; medium correlation with r between ± 0.30 and ± 0.49; small correlation with r under ± 0.29. The P value $p < 0.05$ was considerate significant.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Clinical Hospital of Infectious Diseases and Pneumophysiology 'Dr. Victor Babes' Timisoara (number 10289 / 25th October 2021).

3. Results

3.1 Demographic data

From a total of 19 infants and children with COVID-19 pneumonia admitted to the Clinical Infectious Diseases II and Infectious Diseases - Intensive Care Unit at Clinical Hospital of Infectious Diseases and Pneumophysiology 'Dr. Victor Babes' Timisoara, 10 infants and children (52.63%) were female gender. 12 of them (63.15%) were infants, since 36.84% were children under two years. The mean age is 0.93 ± 0.64, presented as arithmetic mean ± standard deviation (SD), and 95% Confidence Intervals (CI) for the Arithmetic mean was (0.6211 to 1.2400).

The mean weight of subjects included in the study was 9.04 ± 3.08 and 95% CI for the Arithmetic mean was (7.5540 to 10.5302).

Regarding the number of PCR tests performed, the average was 1.63 ± 0.76 and 95% Confidence Intervals (CI) for the Arithmetic mean was (1.2648 to 1.9983). The average for positive PCR tests was 1.42 ± 0.50 and 95% Confidence Intervals (CI) for the Arithmetic mean was (1.1766 to 1.6655).

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The average of hospitalization's days was 4.68 ± 1.73 and 95% Confidence Intervals (CI) for the Arithmetic mean was (3.8486 to 5.5198) since the average of convalescence' s days was was 7.68 ± 2.35 and 95% Confidence Intervals (CI) for the Arithmetic mean was (6.5476 to 8.8209).

All demographic data were summarized in the table below – Table 1.

Table 1. The baseline characteristics of infected infants and children presented as mean ± S.D and 95% CI for the Arithmetic mean

Infants and children' characteristics	Mean ± S.D.	95% CI for the Arithmetic mean
Age	0.93 ± 0.64	0.62 to 1.24
Weight (kilograms)	9.04 ± 3.08	7.55 to 10.53
Total PCR tests	1.63 ± 0.76	1.26 to 1.99
Positive PCR tests	1.42 ± 0.50	1.17 to 1.66
Days of hospitalization	4.68 ± 1.73	3.84 to 5.51
Days of convalescence	7.68 ± 2.35	6.54 to 8.82

3.2 Clinical and biological markers of COVID-19 infection in infants and children under 2 years

The most reliable infants and children's analysed signs and symptoms are presented in Table 2. Also, Table 3 shows biomarkers and paraclinical data for newborns with COVID-19 pneumonia presented as mean SD and 95% CI for the arithmetic mean.

Table 2. The symptoms and comorbidities of infants and children with COVID-19 pneumonia presented as the number of patients and percentage (%) of lot

Infants and children' signs and symptoms	n=19 (percentage %)
General condition moderately influenced	11 (57.89)
General condition slightly influenced	8 (42.10)
Psychomotor agitation	3 (15.78)
Asthenic syndrome	8 (42.10)
Fever (≥ 37.5° C)	16 (84.21)
Cough	12 (63.15)
Rhinorrhea	7 (36.84)
Nasal obstruction	8 (42.10)
Congestive pharynx	14 (73.68)
Dysphonia	4 (21.05)
Dysphagia	2 (10.52)
Red eyes and runny nose	2 (10.52)
Mild acute dehydration syndrome (< 5% of weight)	15 (78.94)
Episodes of diarrhea	3 (15.78)
Diarrhea with bloody stools	1 (5.26)
Vomiting	4 (21.05)

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Loss of appetite	11 (57.84)
Lateral-cervical lymph nodes	3 (15.78)
Dyspnea	1 (5.26)
Glottis spasm	1 (5.26)
Associate pathologies and comorbidities	
Oral candidiasis	3 (15.78)
Lactose intolerance	2 (10.52)
Eggs intolerance	1 (5.26)
Seizures	1 (5.26)
Repeated otitis	1 (5.26)
Atopic dermatitis	1 (5.26)
History of whooping cough	1 (5.26)
Urinarty tract infection	1 (5.26)

Table 3. The biomarkers and paraclinical data of infants and children with COVID-19 pneumonia presented as mean ± S.D and 95% CI for the Arithmetic mean

Biomarker (unit measurement)	Mean ± S.D.	95% CI for the Arithmetic mean
Hemoglobin (g/dl)	11.33 ± 0.98	10.85 to 11.80
Leukocytes (× 10^9/L)	10,334.21 ± 6,960.96	6,979.13 to 13,689.28
Lymphocytes (× 10^9/L)	4,591.05 ± 3,081.92	3,105.61 to 6,076.49
Neutrophiles (× 10^9/L)	4,087.89 ± 4,844.49	1,752.92 to 6,422.86
Monocytes (× 10^9/L)	1,516.84 ± 913.53	1,076.53 to 1,957.15
Thrombocytes (× 10^9/L)	360,000.00 ± 124,869.26	299,814.94 to 420,185.05
Erythrocyte sedimentation rate (mm/h)	17.89 ± 17.64	9.39 to 26.39
LDH (U/L)	279.10 ± 74.29	243.29 to 314.91
AST (U/L)	56.93 ± 35.90	39.62 to 74.23
CRP (mg/L)	20.56 ± 46.22	-1.71 to 42.84
Fibrinogen (g/L) (mg/dL)	3.61 ± 0.99 361 ± 99	3.13 to 4.09 313 to 409
Procalcitonin (ng/mL)	0.28 ± 0.46	0.06 to 0.51
Ferritin (µg/L)	173.07 ± 248.01	53.53 to 292.61
D-dimers (mg/L)	1.03 ± 0.60	0.74 to 1.32
IL-6 (pg/mL)	11.11 ± 9.82	6.38 to 15.85
ALT (U/L)	29.16 ± 20.72	19.17 to 39.15
Urea (mg/dL)	20.78 ± 6.36	17.72 to 23.85
Total bilirubin (mg/dL)	0.24 ± 0.18	0.15 to 0.33

LDH = Lactate dehydrogenase; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; CRP = C-reactive protein.

3.3. Lung ultrasound investigation, score, and correlation

The lung ultrasound technique was used in all cases as an imaging tool for exploring the lung injuries during COVID-19 pneumonia. No other imaging or radiological methods were used for these patients, in accordance with the ALARA principles. Also, the general condition of infants and children did not require any further imaging investigation.

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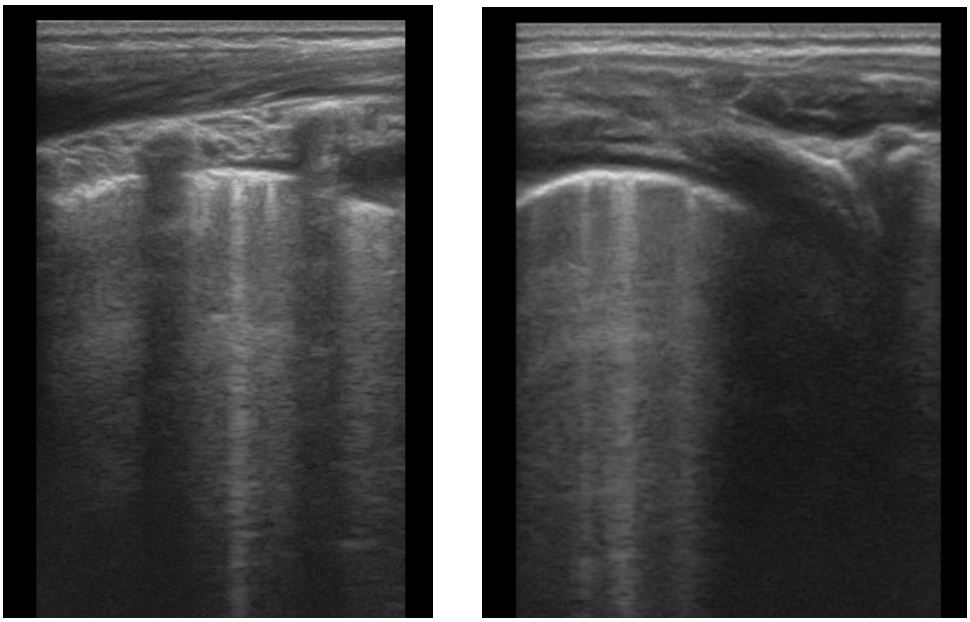
The lung ultrasound examination was performed in the first days (2nd to 4th day) of hospitalization. For 6 infants and children was achieved a second look at lung ultrasound, but only the most representative one was included in the actual study from the point of view of suggestive symptomatology.

The LUS score (LUSS) for each patient varied between 1 to 8 points from a maximum of 36 points. The arithmetic mean was 4.47 ± 2.36 (S.D), while de 95% CI for the Arithmetic mean was 3.33 to 5.61. The area with the highest score recorded was posterior right inferior area (R6) with a mean average = 1 point, followed by posterior left inferior area (L6) with an average of 0.84 points. The lowest scores were recorded in anterior left areas. The main changes described at thoracic ultrasound that appeared in a minimum of one area/children or infants were:

- Disappearance of physiological A-lines – with a prevalence of 100% (n=19);
- Sparse B-lines (Figure 2 a,b) – 100% (n=19);
- Confluent or coalescent B-lines (Figure 3 a) – 36.84% (n=7);
- Pleural abnormalities (irregularities, thickening, fragmented) – 42.10% (n=8);
- Subpleural consolidation < 1 cm (Figure 3 b) – 21.05% (n=4);
- Pleural effusion – 5.26% (n=1).
- There was not reported any large consolidation in the subjects included.



(**a**) (**b**)

Figure 2. The lung ultrasound showed **(a)** sparse B-lines with small zones of pleural irregularities corresponding to a LUSS =1; **(b)** sparse B-lines with small zones of pleural irregularities corresponding to a LUSS =1, and a small transonic fluid acumulation.

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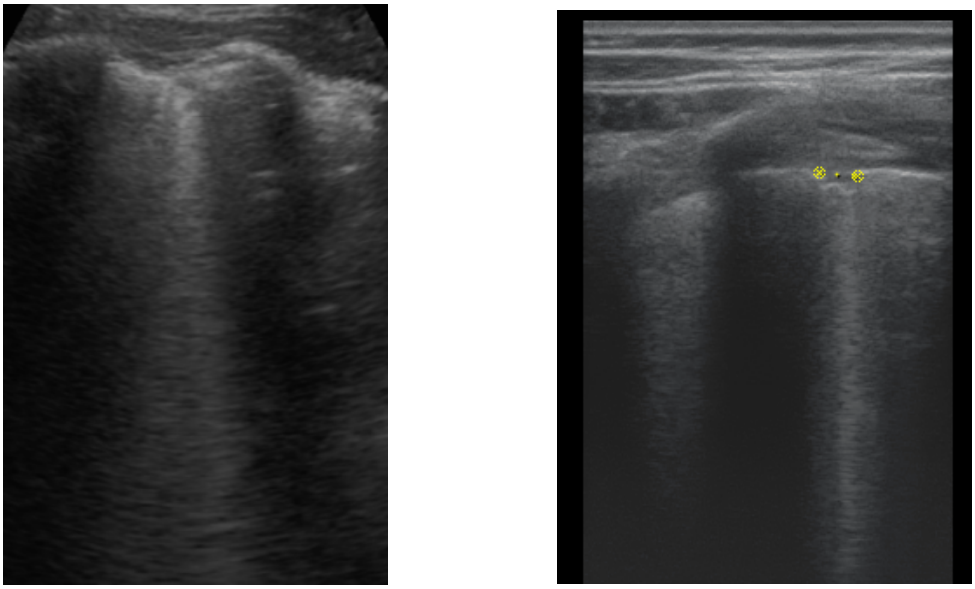

(**a**) (**b**)

Figure 3. **(a)**; **(b)** The lung ultrasound showed a small consolidation area with the length < 1 cm and with associated pleural abnormalities corresponding to a LUSS=2

The relationship between manifestations or symptoms and LUSS was documented through statistical tests, using Chi-squared test ($\chi 2$). Moreover, another Chi-squared test between days of hospitalization and LUSS revealed $\chi 2 = 55.41$, DF = 42, contingency coefficient = 0.863 and with a significance level p=0.08 (Figure 4). Regarding the Chi-squared test between days of convalescence and LUSS, the significance level P was lower in statistical power (p=0.11).

Chi-squared test for the trend between cough (present=1/absent=0) and LUSS has proved that the $\chi 2$ trend was 5.46, DF=1 with p=0.01 (Figure 5a), while the Chi-squared test between cough (present/absent) and LUSS has revealed that the $\chi 2 = 8.25$, DF=7 with p=0.31. Chi-squared test for the trend between fever (present=1/absent=0) and LUSS has proved that the $\chi 2 = 6.46$, DF=7 with p=0.48, while the relationship between psychomotor agitation and LUSS showed $\chi 2$ test was 4.58, DF=7 with p=0.71.

Assuming equal variances, the difference of an independent t-test between the LUSS for children who presented cough (n=12) and LUSS for children without cough (n=7) was –2.55, with a 95% confidence interval from -4.62 to -0.49; the t-test statistic was -2.61, with 17 degrees of freedom (DF) and an associated two-tailed probability P-value p=0.01 (Figure 5b). There was not any statistical difference between the LUSS for children who presented fever (n=16) with arithmetic mean (a.m.) for this sample = 4.56 and LUSS for children without fever (n=3) with a.m.= 4, with T-test p=0.71.

Pearson's correlation coefficient r between the LUSS and the main biomarkers of inflammations/infections were:

- r=0.46 (p=0.04, 95% CI 0.018 to 0.761) between the LUSS and LDH level;
- r=0.66 (p=0.01, 95% CI 0.147 to 0.896) between the LUSS and LDH level at symptomatic infants and children (with cough present) – figure 6a;
- r=0.47 (p=0.06, 95% CI -0.030 to 0.784) between LUSS and LDH level at symptomatic infants and children (with fever present);

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- r=0.36 (p=0.12, 95% CI -0.103 to 0.704) between the LUSS and AST (Aspartate aminotransferase) level;
- r=0.58 (p=0.008, 95% CI 0.184 to 0.823) between the LUSS and D-dimers level – figure 6b;
- r=0.66 (p=0.01, 95% CI 0.140 to 0.895) between LUSS and D-dimers level at symptomatic infants and children (with cough present) – figure 6c;
- r=0.50 (p=0.04, 95% CI 0.017 to 0.802) between LUSS and D-dimers level at symptomatic infants and children (with fever present);
- r=0.55 (p=0.013, 95% CI 0.136 to 0.806) between the LUSS and IL-6 level – figure 6d;
- r=0.38 (p=0.21, 95% CI -0.243 to 0.785) between LUSS and IL-6 level at symptomatic infants and children (with cough present);
- r=0.38 (p=0.13, 95% CI -0.133 to 0.740) between LUSS and IL-6 level at symptomatic infants and children (with fever present);
- r= -0.68 (p=0.001, 95% CI -0.869 to -0.335) between LUSS and O_2 saturation level - figure 7.

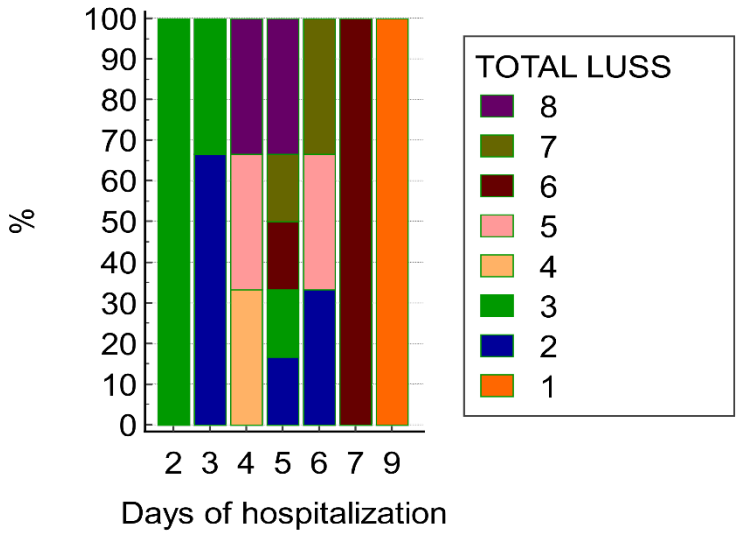

Figure 4. The relationship between days of hospitalization and LUSS - the frequencies chart of Chi-squared test with a graph with 100% stacked column

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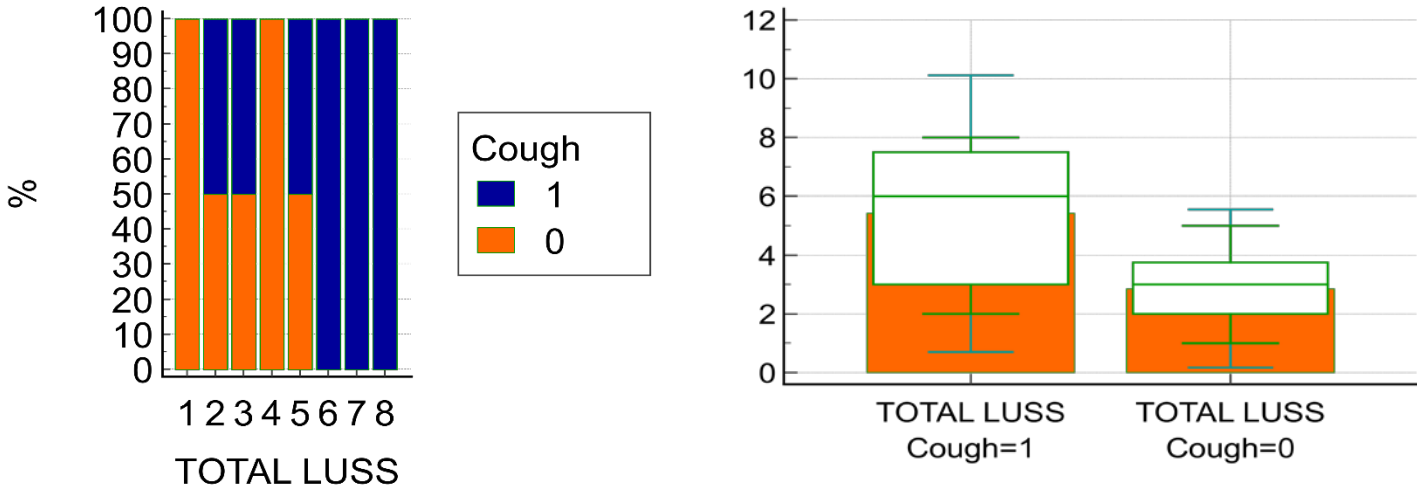
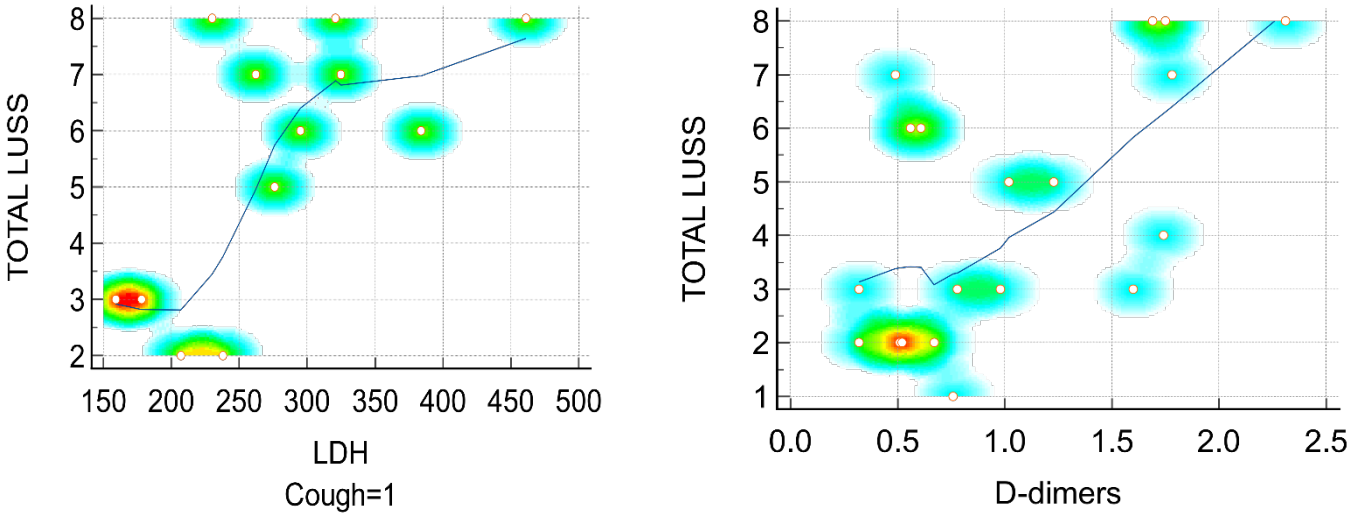


(**a**) (**b**)

Figure 5. The relationship between symptoms (cough) and LUSS; 1 means presence/affirmative and 0 means absence/negative **(a)** the frequencies chart of Chi-squared test with a graph with 100% stacked column; **(b)** Box-and-whisker of data comparison between LUSS at infants and children with cough and LUSS at infants and children without



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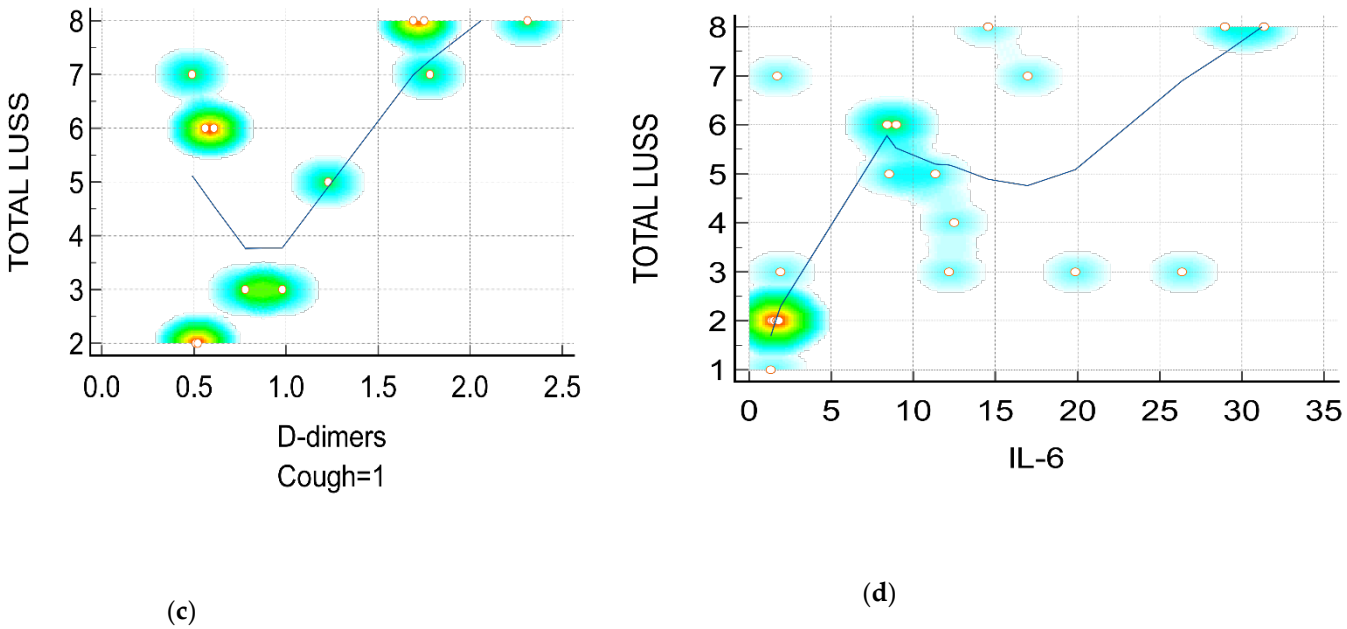

(**c**) (**d**)

Figure 6. Scatter diagram with heat map of correlation between LUSS and biomarkers: (a) LUSS and LDH level at infants and children who presented cough; (b) LUSS and D-dimers level from all subjects; (c) LUSS and D-dimers level from the subjects who presented cough; (d) LUSS and IL-6 level – all positive linear correlation.

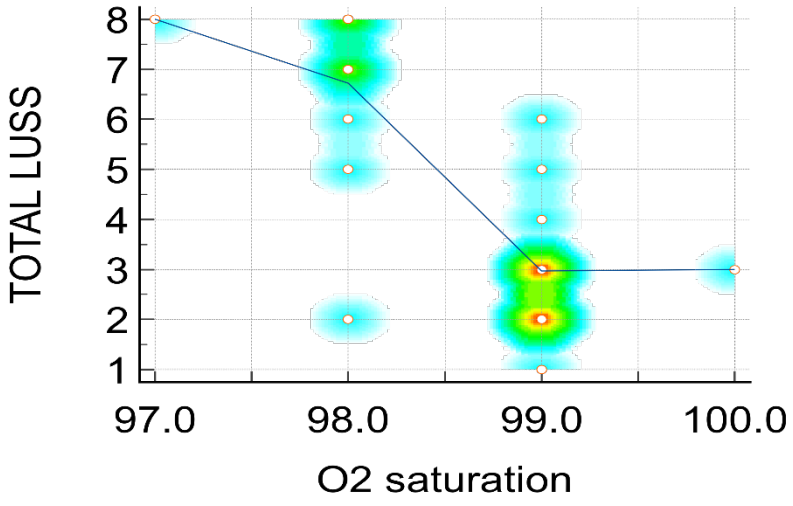

Figure 7. Scatter diagram with heat map of correlation between LUSS and O_2 saturation – negative linear correlation.

4. Discussion

None of the children included in the research needed orotracheal intubation or oxygen administration, due to the fact that all of them had mild to moderate forms of the disease. There are a few studies that support this supposition, such as Jackson et al. who concluded in their review that the risk of developing severe illness or death in children

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is low **[11]**. Moreover, one multicenter that included a number of 91 children cases with COVID-19 pneumonia concluded that it is unnecessary to perform invasive or irradiating chest imaging in children, because most of their evolution will be with mild symptoms, mostly fever and cough **[7]**. This fact was the motivation of our study, for investigating the infants and small children with a non-invasive and non-irradiating method, like lung ultrasound technique.

Unlike in adults, whom have a higher risk of developing aggressive forms of disease, and require more hospitalization days, most of the children in our study needed less than 5 days of hospital admission **[12]**. Furthermore, here occurs another reason for this short hospitalization of the included infants and children, 52.63% of mothers or caregivers decided that they want a discharge on request, contrary to the advice of the doctor. Otherwise, probably the Chi-squared test between days of hospitalization and LUSS would have had a better statistical power than the current ones ($\chi 2 = 55.41$, p=0.08).

The most common symptoms our patients developed were fever, mild acute dehydration syndrome, congestive pharynx, cough, loss of appetite, and influenced general condition (moderately to slightly). These data were also find by Mansourian et al. in their review on 32 articles **[13]**. On the other hand, diarrhea with bloody stools and dyspnea were present in only one patient from our study (5.26%), while runny nose and red eyes were found in 10.52% of the patients. These results are resembling to the ones found by Mansourian et al. **[13]**. Moreover, a large study involving more than 5000 children and more than 1000 infants and children under 2 years old, revealed a prevalence of fever in the group <1 years and 1-4 years between 64.8 – 77.2%, which is comparable with our results **[14]**. Also, cough was found with a prevalence between 53.1 – 65.5% in their study, which fits exactly with the prevalence of cough from our study (63.15%) **[14]**.

The clinical parameters and symptoms for defying a pulmonary involvement, like cough had a similar imaging value for lung lesions, according to t student test results (the difference was –2.55 with an associated p=0.01). Thus, the children with symptoms (cough present) had a mean average of LUSS (5.41) higher than the mean average of LUSS in ones without symptoms (2.87), statistically significant.

The inflammatory probes revealed the biological status of infants and children. They have been analyzed to all intents and purposes, taking in account leukocytes, lymphocytes, neutrophiles, monocytes, thrombocytes, ESR, LDH, AST, CRP, fibrinogen, procalcitonin, ferritin, D-dimers, and IL-6. From all laboratory findings, LDH, D-dimers and IL-6 levels have been corelated with the lung ultrasound score with higher statistical evidence. The Pearson's correlation coefficient r between the LUSS and LDH level for symptomatic (with cough) infants and children was r=0.66 with p=0.01, which demonstrates a strong positive correlation. Additionally, the correlation coefficient r between the LUSS and D-dimers level was 0.58 with p=0.008 for all subjects included, while r= 0.66 with p= 0.01 was shown between LUSS and D-dimers level for symptomatic ones (with cough), demonstrating a linear strong positive correlation. Also, the same correlation was demonstrated between the LUSS and IL-6 levels, a fact already proved in the study based on newborns with COVID-19 pneumonia **[4]**.

Regarding some blood parameters compared with another study that included children, the mean value of leukocytes for our study was 10,334.21 ± 6,960.96, compared to 8880 ± 1086 in Musolino et al.' study. Neutrophiles' mean value in actual study was 4,087.89 ± 4,844.49, compared with a higher mean value 7023 ± 996. Also, lymphocytes mean value is higher (4,591.05 ± 3,081.92), compared with a considerably lower mean value of 1057 ± 112. Regarding the inflammatory status, CRP level was lower (11.44 ± 1.8) compared with the actual study result of 20.56 ± 46.22 mg. These variations could be from multisystemic inflammatory disease during SARS-CoV2 infection and other associated pathologies of the children included **[15]**.

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The relationship between LUSS and O_2 saturation was a strong linear negative one with r= -0.68 (p=0.001, 95% CI -0.869 to -0.335), which can be considered an important parameter that must be explored in respiratory pathologies, especially in COVID-19 pneumonia in infants and small children. Moreover, this strong negative correlation was found in the study conducted on the newborns with SARS-CoV2 infection **[4]**.

According to Buonsenco and Vertungo, lung ultrasound made important steps in becoming a reliable imaging method in respiratory pathologies, for both adults and children **[3]**. Moreover, Vertungo et al. described four different types of evolution, comparing the symptoms of patients and their imaging progress **[16]**. One of these phenotypes, specifically the 1st and 4th ones, it seems to be consistent with what happens to infants and small children. The 1st phenotype describes subjects whose clinical improvement is independent of the LUS progression, since the 4th phenotype includes patients with an improvement on their clinical condition, but without such a response, concurrently in the evaluation score of the injured lung. Probably, this is the reason of a strong correlation between the LUSS and just a few of the inflammatory biomarkers demonstrated in this study (LDH, D-dimers, IL-6).

The appearance of sparse B-lines in minimum one evaluated area was the most common finding in lung ultrasound of included subjects with a prevalence of 100%. These results are in accordance with the results from Musolino et al.' study and the study that included newborns with COVID-19 pneumonia, with the same prevalence of sparse B-lines **[4,15]**. Another systematic review found a prevalence of sparse B-lines of 50%, instead of the subjects' status (6.81% asymptomatic and 81.81% with mild to moderate symptoms) **[8]**.

The aspect of confluent or coalescent B-lines with the prevalence of 36.84% is lower than the prevalence from Musolino et al.' study (80%) described as multiple/severe B-lines and also lower than the category described as white lung (50%) **[15]**. Also, this discrepancy in the results could be because of the severity of the included subjects with additionally difference between LUSS mean value of 10.5 ± 1.81 compared to our study - 4.47 ± 2.36. But, our result is in accordance with Caroselli et al, who found in their review a prevalence of coalescent B-lines of 25% **[8]**. Also, pleural abnormalities (irregularities, thickening, fragmented) are pretty much similar with Caroselli et al.' review (42.10% in our study compared to 34.09% for pleural irregularities + 4.55% described as thickening of the pleural line in their review) **[8]**.

More articles found the pleural effusion in evolution of COVID-19 pneumonia in children as a very rare alteration appeared in lung ultrasound technique **[4,7,8]**. Our study strengthens these results.

Many studies have concluded that the peripheral spaces from posterior inferior areas are most affected by COVID-19 pneumonia, both in children and adults **[2,3,7,8,15]**. The mean value of LUSS in our study was higher in the posterior right inferior area and posterior left inferior area, in accordance with the results presented above.

Limitation of study/ Weakness

One of the limitations of the study is the fact that while most of the patients did not come back for follow-up, some of them were even discharged earlier than recommended, on request. Monitoring through ultrasound the changes found on the admission would be beneficial. Other limitation is the number of subjects included in the study. A more significant statistical result would be found if the group of patients was larger, and the correlations would have been better and stronger.

Further directions

Several future directions can be implemented, such as finding stronger correlations between lung ultrasound changes and biomarkers, in different respiratory pathologies. Other future direction that can be insisted on is the follow-up of patients with respirato-

ry pathologies, to observe the lung changes in dynamic, taking into account the fact that lung ultrasound is a non-irradiating imaging method and a repeatable one. Moreover, according to Buonsenco and Vertungo, the important steps were already done in order to make LUS a reliable tool in lung changes associated with respiratory pathologies **[3]**. The next step is finding a score of severity based on LUSS, biomarkers and symptoms for a better evaluation of the patients.

5. Conclusions

The trustworthy correlation between lung ultrasound score and highly sensitive inflammatory markers like LDH, D-dimers and IL-6 levels could suggest further use of LUSS in monitoring inflammatory lung diseases. With current advances, soon, lung ultrasound could be used as a non-irradiating, repeatable surveillance method in infants and children affected by pneumonia and other respiratory pathologies.

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