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The Diagnostic Value of Lung Ultrasound in Neonates and Infants with Acute Bronchiolitis

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Abstract

Objective – We analysed the relationship between the lung ultrasound (LUS) score and clinical characteristics in order to evaluate the diagnostic and predictive value of LUS in neonates and infants with acute bronchiolitis. **Subjects and Methods** – Term infants aged up to 3 months, admitted to Ljubljana University Children's Hospital due to acute bronchiolitis in the period from January to April 2020, were studied prospectively. LUS score and clinical assessment score (CAS) were determined upon admission. The patients were divided into groups according to LUS score and CAS. Clinical and laboratory characteristics were compared between the groups. Correlations between LUS score, duration of clinical signs prior to admission, CAS and partial carbon dioxide pressure in the capillary blood (PCO_2) upon admission, length of hospitalization and duration of supplemental oxygen (O_2) therapy were analysed. Additionally, the predictive value of LUS and CAS for the need of non-invasive respiratory support (NRS) was calculated. **Results** – The LUS score correlated with the clinical severity of acute bronchiolitis. Patients with higher LUS score had higher CAS (P<0.001) and PCO_2 upon admission (P=0.014), and needed O_2 therapy for a longer time (P=0.023). These patients also required NRS (P=0.024) more often, were positive for respiratory syncytial virus (P=0.008), and had a chest X-ray performed (P<0.001). The LUS score correlated well with CAS (P<0.001, r=0.762). LUS score at admission underperformed to identify subsequent NRS treatment needs (AUC 0.76 (0.54-0.97), P=0.069) compared to CAS (AUC 0.85 (0.68-1.00), P=0.013). **Conclusions** – Larger studies are needed to evaluate the predictive and diagnostic value of LUS in neonates and young infants with acute bronchiolitis.

Key Words: Clinical Assessment Score ▪ Lung Ultrasound Score ▪ Non-Invasive Respiratory Support ▪ RSV ▪ Ultrasonography.

Introduction

Acute bronchiolitis is diagnosed clinically, and additional imaging studies are only seldom indicated. Nevertheless, chest X-ray (CXR) is often performed in infants with acute bronchiolitis (1). Lung ultrasound (LUS) is a promising imaging tool in clinical practice and its use has increased in the last decade, although conclusive data in this field are still missing (2).

Ultrasound imaging is based on the differences in echogenicity between tissues. Well-ventilated lungs have high acoustic impedance, thus limiting actual tissue visualisation. However, the hyperreflective pleural line and its distal ultrasound-related reverberation artefacts (A lines) can be visualised (2). Healthy lungs are further characterized by the sliding of visceral and parietal pleura during breathing, seen on LUS as the sliding of hyperechoic lines next to each other.

Increased pulmonary interstitial fluid content can be detected as vertical artefacts, known as B lines, reflecting changes in the pleuro-parenchymal interface. A large number of B lines may coalesce

in a confluent pattern, known as white lung. This is a sign of disease progression due to an increased proportion of fluid in the lungs, and is indicative of the development of alveolar-interstitial syndrome (3–5). Consolidations adjacent to the pleural line resulting from lung dysventilation have hypoechoic heterogeneous echotexture, with a tissue-like pattern.

LUS has proven accurate in diagnosing pneumothorax, pleural effusion, pneumonia and lung oedema in children and adults (6, 7). Moreover, in premature infants LUS is useful in assessing surfactant needs in respiratory distress syndrome (8) in mechanically ventilated neonates (9), and diagnosis of transient neonatal tachypnoea (10). Few studies have evaluated LUS for diagnostics and management of acute bronchiolitis in infants. So far it has not been implemented as a standard of care for neonates with acute bronchiolitis. Recently its use has been recommended for descriptive purposes in viral bronchiolitis by the European Society of Paediatric and Neonatal Intensive Care, although it is said that it cannot provide a differential aetiological diagnosis (11).

The aim of this study was to assess the diagnostic value of LUS in neonates and infants with acute bronchiolitis, and to evaluate its predictive value for the needs of non-invasive respiratory support (NRS).

Subjects and Methods

Selection of Participants

This prospective cross-section observational study was conducted at the Neonatal and Paediatric Pulmonology Department, Ljubljana University Children's Hospital. The consecutive inclusion of neonates and infants ≤ 3 months old hospitalized due to acute bronchiolitis started at the beginning of January 2020 and was stopped at the end of April due to COVID-19 pandemic. Children with congenital anomalies, chronic lung disease (CLD), neurological conditions and prematurity were excluded.

Methods

At the time of admission each patient was evaluated by the admitting paediatrician using the clinical assessment score (CAS). Pulse oximetry (SpO_2) was measured using Masimo transcutaneous oximeter Radical-5 with the neonatal measuring sensor strip fixed to one of the feet or hands. It was measured at the time of admission to the hospital and during hospitalisation, according to the standard hospital protocol.

LUS was performed within 24 hours, usually immediately after the admission by a single neonatologist JLK. LUS was performed with an Esaote ultrasound MyLab 9eXP using a 4–15 MHz linear probe (probe L 4–15). The LUS examination took place at the bedside, following the principles of individualized neonate and infant-friendly care. A standard heated ultrasound gel was used, patients were in a supine position, lying slightly on the opposite side of the view taken. Management of patients continued according to the standard hospital protocol. Chest X-ray (CXR) was performed at the attending paediatrician's discretion.

Clinical Assessment Score

CAS was adapted from a previously published protocols (2, 6). The values of oxygen saturation measured by SpO_2 at the time of the first assessment were included in the CAS (12). CAS consisted of the age adjusted respiratory rate, use of accessory respiratory muscles, signs of dyspnoea, lung auscultation results, and SpO_2 at the time of admission (Table 1). The CAS was obtained by clinical assessment and examination by the admitting physician. The sum of all CAS points provided an objective level of disease severity. Accordingly, patients were divided into 3 groups: (i) 1–5 points – mild bronchiolitis, (ii) 6–10 points – moderate bronchiolitis and (iii) 11–15 points – severe bronchiolitis.

To estimate the reliability of the CAS, we compared the clinical indicators of the severity of the disease and laboratory results between different bronchiolitis severity groups, divided by the CAS scores. The clinical variables used were: pH, PCO_2,

Table 1. Clinical Assessment Score for Acute Bronchiolitis Used in the Study

Variable		Number of points			
Main	Age	0	1	2	3
Respiratory rate	<2 m		≤ 60	61–69	≥ 70
	2-12 m		≤ 50	51–59	≥ 60
Use of accessory respiratory muscles		Without	Subcostal or intercostal	2 of the following: subcostal, intercostal, substernal or fluttering nostrils	3 of the following: subcostal, intercostal, substernal, suprasternal, supraclavicular or fluttering nostrils, nodding of the head in the rhythm of breathing
Dyspnoea		Normal feeding, vocalization and activity	1 of the following: feeding problems, decreased vocalization, agitation	2 of the following: feeding problems, decreased vocalization, agitation	No feeding, no vocalization, sleepy or confused
Auscultation		Normal breathing, no wheezing	Late-expiratory wheeze or crackles	Pan-expiratory wheeze or crackles	Inspiratory and expiratory wheezes or crackles or reduced respiratory sounds
SpO_2* on admission		>94%	94–92%	92–88 %	<8 %

*Oxygen saturation measured by pulse oximetry.

SpO_2, duration of oxygen (O_2) therapy in days, respiratory support, xanthine derivative treatment used, parenteral hydration treatment, proportion of CXR performed and the type of viral agent detected.

LUS Assessment Score

For research purposes, a semiquantitative LUS score was adapted from previously published protocols (2, 13). Each lung was divided into 6 segments: (i) anterior superior, (ii) anterior inferior, (iii) lateral superior, (iv) lateral inferior, (v) posterior superior, and (vi) posterior inferior, creating a total of 12 separately graded regions. Each region was examined individually, looking for signs of bronchiolitis, and then graded with 0–2 points according to the LUS score grading system (Table 2). The sum of all 12 parts from both lungs gave a final LUS score in the range of 0–24 points. Patients were divided into three groups according to the LUS score results: (i) 1–8 points – Group 1 (mild lung impairment), (ii) 9–16 points – Group 2 (moderate lung impairment) and (iii) 17–24 points – Group 3 (severe lung impairment).

Clinical Data

Other clinical and laboratory data were obtained and analysed: duration of clinical signs before admission, duration of O_2 treatment in days, mode of respiratory support (O_2 supplied by nasal cannula, NRS, invasive ventilation), xanthine derivative treatment used, parenteral hydration, viral agent detected, capillary blood gas analysis and CXR performed, if available, and hospitalization length.

Table 2. Lung Ultrasound Score by Lung Field Used in the Study

LUS* examination	Points
Normal or mild interstitial pattern (<3 B lines)	0
Interstitial pattern (>3 B lines or white lung) or subpleural consolidations <1 cm	1
>1 cm subpleural consolidation (bronchogram +/-, atelectasis) or consolidation regardless of size with effusion	2

*Lung Ultrasound Score.

Ethics Statement

This study was approved by the National Medical Ethics Committee (0120-477/2019/5). Informed consent was obtained from all the parents of participating children prior to inclusion in the study.

Statistical Analysis

Descriptive statistics, means, medians, value ranges, standard deviations (SD), interquartile distances, and confidence intervals were used to describe the study sample. The study patients were divided into three groups according to the CAS. According to the LUS, two study groups were formed since none of the patients met the criteria for the 3rd LUS group. A non-parametric test was used to test the differences in pH, PCO_2, SpO_2 at admission, and duration of O_2 therapy in days between the LUS and CAS groups. Additionally, a non-parametric test was used to test the differences in LUS score between different CAS groups. The non-parametric tests were used in these cases since the assumption of normality of the distribution has been violated. Fisher's exact test was used to analyse the differences in proportions of the mode of respiratory support, patients receiving xanthine derivative treatment and parenteral hydration, CXR performed, and viral agents isolated between the LUS and CAS groups. Student's t-test was performed to test the statistical significance of the differences in the CAS between the LUS groups. Pearson's correlation coefficient was used to evaluate the correlation between LUS and CAS, duration of O_2 therapy, duration of clinical signs before admission, hospitalization length and PCO_2 upon admission. To analyse the clinical applicability of CAS and LUS in predicting the need for NRS, we used a ROC (receiver operating characteristic) curve. In addition to the AUC (area under the curve), it also provided us with delimiter points and their sensitivity and specificity. On the basis of the ROC analysis, we determined the optimal delimitation values of both scores to predict the need for NRS. Additionally, in order to estimate the accuracy of LUS and CAS in predicting necessity of NRS we performed the cross-validation using the leave-one-out cross-validation (LOOCV), suitable for small samples. Statistical analysis was performed using the statistical package IBM SPSS Statistics, version 25 (IBM Corporation, Armonk, USA) and Excel, version 365 (Microsoft, Redmond, USA). For the limit of statistical characteristics, a value of $P<0.05$ was used in all tests.

Results

During the study period, 19 neonates - 9 (47%) male, whose parents consented to participation in the study met the inclusion criteria. Their demographic and clinical characteristics are presented in Table 3.

The proportion of patients needing O_2 therapy and NRS is shown in Table 4. Two patients who needed NRS required continuous positive airway pressure (CPAP), two needed high flow nasal cannula (HFNC), one CPAP and bi-level positive airway pressure ventilation (BiPAP), one CPAP and

Table 3. Clinical Characteristics of the Studied Cohort

Characteristic (unit)	
Age at admission (day), median (95 % CI*)	18 (6–30)
Birth weight (g), mean (95% CI*)	3583 (3260–3905)
Apgar 5 min, mean (95% CI*)	9.2 (8.9–9.4)
Time from onset of disease to hospitalisation (day), mean (95% CI*)	4.1 (2.4–5.7)
Hospitalisation duration (day), mean (95% CI*)	6.7 (5–8.4)
Parenteral hydration treatment used, N† (proportion)	16 (84%)
Xanthine derivative treatment used, N† (proportion)	4 (21%)

*Confident interval; †Number of patients.

Table 4. The Need for Oxygen Therapy and Non-invasive Respiratory Support in the Studied Cohort

Oxygen therapy	Number of patients (%)	Average amount of O_2 added (95% CI*)
Without O_2 treatment	4 (21)	-
Nasal cannula - O_2 flow L/min	8 (42)	0.5 (0.20–0.98)
Non-invasive respiratory support - FiO_2	7 (37)	0.5 (0.28–0.73)

*Confident interval.

HFNC and one CPAP, BiPAP and HFNC. The average duration of O_2 treatment was 3.3 days (95% CI 2.2, 4.5).

CAS and LUS Score

According to the CAS, three groups were formed: 6 patients had mild bronchiolitis, 8 moderate and 5 severe. According to the LUS score, 8 patients were classified in Group 1, 11 patients in Group 2, while no one was classified in Group 3. The clinical and laboratory characteristics of the patients, grouped according to the CAS, are presented in Table 5. Children with a more severe grade of bronchiolitis had a higher level of PCO2 at admission (P=0.014) and a higher LUS score (P=0.042), they needed treatment with O_2 longer (P=0.023), the causative viral agent was more likely to be respiratory syncytial virus (RSV) (P=0.002), and they underwent CXR more frequently (P=0.001).

The clinical and laboratory characteristics of patients grouped according to the LUS score are presented in Table 6. Children in the LUS group 2 had higher CAS (P <0.001), higher levels of PCO_2 at admission (P=0.014), needed treatment with O_2 longer (P=0.023), the causative viral agent was more likely to be RSV (P=0.008) and they needed NRS more frequently (P=0.024). Using Pearson's

Table 5. Clinical Characteristics of Patient Groups according to Clinical Assessment Score

Clinical parameter				
Degree of bronchiolitis	Mild (N=6)	Moderate (N=8)	Severe (N=5)	P
LUS* points (median; IQR†)	6.5 (6–7)	10.5 (8.75–12)	10 (9–12)	0.041‖
pH (median; IQR†)	7.369 (7.363–7.374)	7.377 (7.373–7.384)	7.407 (7.377–7.419)	0.230‖
PCO_2 kPa (median; IQR†)	5.79 (5.79–6.53)	6.92 (6.84–7.23)	6.14 (5.19–7.18)	0.014‖
SpO_2 % (median;IQR†)	95.5 (94.3–97.5)	88.5 (86.3–94.3)	90.0 (75.0–94.0)	0.184‖
O_2 treatment days (median; IQR†)	1 (0–2)	4 (2.75–6)	6 (4–6)	0.023‖
Respiratory support	N (%)			
None	3 (50)	1 (12.5)	0 (0)	
O_2 by nasal cannula	3 (50)	3 (37.5)	2 (40)	0.131¶
Non-invasive respiratory support	0 (0)	4 (50)	3 (60)	
Xanthine derivative treatment used (yes)	0 (0)	2 (25)	2 (40)	0.312¶
Parenteral hydration used (share)	4 (66.7)	7 (87.5)	5 (100)	0.438¶
CXR‡ performed (yes)	0 (0)	7 (87.5)	5 (100)	0.001¶
The viral agent	N (%)			
None	4 (66.7)	0 (0)	0 (0)	
RSV§	1 (16.7)	7 (87.5)	5 (100)	0.002¶
Rhinovirus	1 (16.7)	1 (12.5)	0 (0)	

*Lung ultrasound; †Interquartile range; ‡Chest X-ray; §Respiratory syncytial virus.m ‖Calculated by a non-parametric median comparison test. ¶Calculated by Fisher's exact test.

Table 6. Clinical Characteristics of Patient Groups according to Lung Ultrasound Score

Clinical parameters	Groups by LUS		
	Group 1 (N=8)	Group 2 (N=11)	P
CAS* (average; IQR†)	4.5 (2.75–5.5)	10.64 (9.5–12)	<0.001‡
pH (median; IQR†)	7.371 (7.365–7.376)	7.384 (7.373–7.409)	0.230§
PCO_2 kPa (median; IQR†)	5.85 (5.82–6.58)	6.90 (6.50–7.11)	0.014§
SpO_2 (median; IQR†)	95.50 (94.0–98.0)	89.00 (82.5–94.0)	0.184§
O_2 treatment days (median)	1 (0–2)	5 (3.5–6)	0.023§
Respiratory support	N (%)		
None	4 (50)	0 (0)	0.024‖
O_2 by nasal cannula	3 (37.5)	5 (45.5)	
Non-invasive respiratory support	1 (12.5)	6 (54.5)	
Xanthine derivative treatment used (yes)	1 (12.5)	3 (27.3)	0.603‖
Parenteral hydration used (yes)	6 (75)	10 (90.9)	0.546‖
CXR performed (yes)	1 (5.3)	11 (57.9)	<0.001‖
The viral agent	N (%)		
None	4 (50)	0 (0)	0.008‖
RSV	3 (37.5	10 (90.9)	
Rhinovirus	1 (12.5)	1 (9.1)	

*Clinical assessment score; †Interquartile range; ‡Calculated by Student's t test for independent samples; §Calculated by non-parametric median comparison test; ‖Calculated by Fisher's exact test.

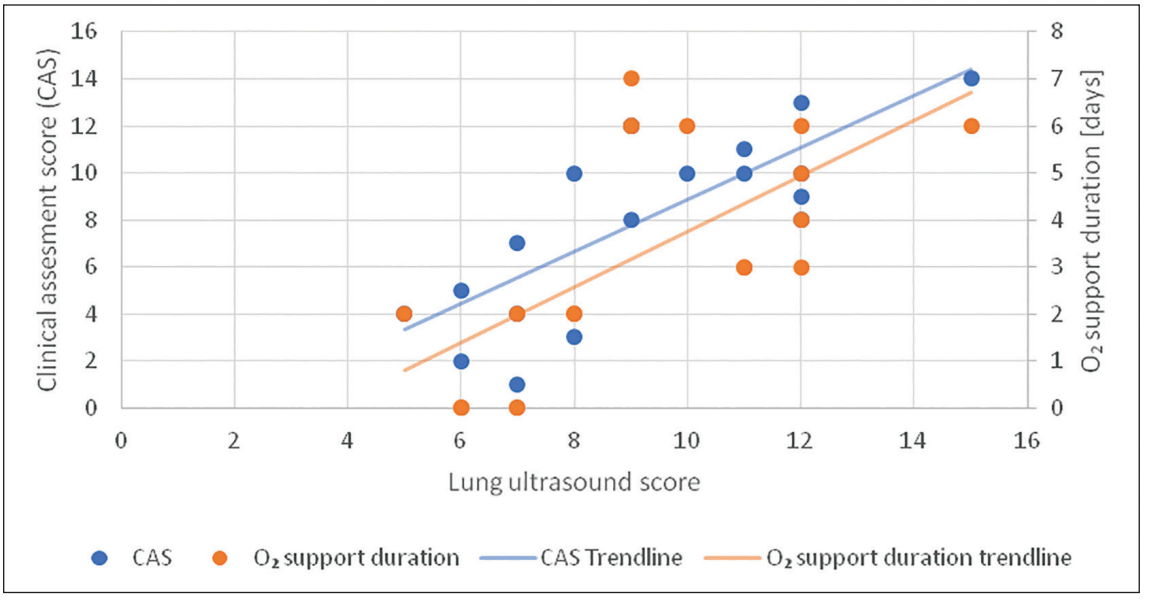

Fig. 1. *Lung ultrasound score compared to clinical assessment score and duration of O_2 support.*

correlation coefficient, the LUS score was shown to correlate well with the CAS (P<0.001, *r*=0.762) and the duration of O_2 therapy (P=0.002, *r*=0.654) (Fig. 1), but it did not correlate with the duration of clinical signs before admission, hospitalization length and PCO_2 level upon admission.

Prediction of NRS from LUS and CAS

The difference between the LUS score groups regarding the need for NRS was statistically significant (P=0.024). Patients with a higher CAS required NRS more frequently, although the difference between the CAS groups was not statistically significant. We aimed to analyse the predictive value of LUS and CAS upon admission for identification of patients who would need NRS. We used ROC curve analysis and determined the AUC, and the specificity and sensitivity of the optimal delimitation value for both LUS and CAS. The analysis of both ROC curves showed that the AUC of the CAS was higher (AUC 0.85 (0.68–1.00), P=0.013) compared to the AUC of the LUS score (AUC 0.76 (0.54–0.97), P=0.069).

On the basis of the ROC analysis we determined the optimal discriminative values for both scores to be 8.5. LUS score ≥9 points reached 85% sensitivity and 58% specificity to predict the use of NRS. Positive predictive value (PPV) for LUS score ≥9 was 0.55 and negative predictive value (NPV) was 0.88. If LUS score ≥8 points is used, sensitivity increases to 100 %, while specificity decreases to 50%. If LUS score ≥10 points is used sensitivity decreases to 57%, while specificity increases to 67%. CAS ≥9 points predicted the use of NRS with higher accuracy, since it reached 85% sensitivity and 67% specificity. PPV was 0.6 and NPV was 0.89. If CAS score ≥8 points is used, sensitivity increases to 100%, while specificity decreases to 58%. If LUS score ≥10 points is used sensitivity remains at 85%, while specificity increases to 75%.

The misclassification rate in predicting the NRS with CAS is 26.3%, and with LUS 31.6%. The cross-validation using the LOOCV shows rather stable results of misclassification when NRS is predicted with LUS (the average misclassification in random samples of 18 units is 31.6%, with a SD of 2.6%) and with CAS (the average misclassification is 25.7%, with a SD of 2.7%).

Discussion

In our study, we addressed the diagnostic and predictive value of LUS for acute bronchiolitis in neonates and infants <3 months of age. Children with higher LUS scores upon admission had a more severe disease, as they had a higher CAS score, required longer O_2 therapy, had poorer capillary blood gas analysis results upon admission, and required NRS more often. Moreover, the LUS score correlated strongly with CAS. On the other hand, the predictive value of LUS to identify patients who needed NRS was not satisfactory.

The applicability of LUS in paediatrics has been the subject of debate for many years (10). Although LUS is not part of the currently established clinical management of acute bronchiolitis, there is emerging evidence of several possible roles of LUS in acute bronchiolitis. LUS could help to determine the severity of the disease, predict the need for hospitalisation or respiratory support, and diagnose complications such as atelectasis, pneumonia etc.

Other researchers had addressed the diagnostic and predictive value of LUS in bronchiolitis. Basile et al. found that LUS correlated with clinical evaluation and the need for O_2 supplementation, and had high specificity for identifying infants who needed supplementary O_2 (2). Similarly, in the study by di Mauro et al. the LUS score was associated with the need for supplemental O_2 and the duration of hospital stay, while it was not associated with the duration of O_2 therapy (14). In the study by La Regina et al. the LUS score correlated positively with the clinical score, similarly to our study, but also with the length of hospitalisation, a correlation which we did not detect (15). Also, Supino et al. confirmed the higher LUS score in infants who needed respiratory support or CPAP compared to infants which didn't need any respiratory support (16). LUS was detected as the most effective parameter in determining hospital admission in a prospective observatory study from Turkey (P=0.044; adjusted odds

ratio, 1.859; 95% CI 1.016–3.404) (17). A prospective Dutch study by Ingelse et al. investigated the link between LUS and the oxygenation anomaly in paediatric intensive care unit patients who required invasive mechanical ventilation. They showed that, in severe forms of bronchiolitis, the LUS correlated positively with the O_2 saturation index, but only in the acute phase of the disease (18).

The role of LUS in the identification of complications of bronchiolitis was not addressed in our study, and there are also limited data on this subject in the literature. Biagi et al. compared the diagnostic accuracy and reliability of LUS with CXR for the detection of pneumonia in children with bronchiolitis. They showed the good accuracy (100% sensitivity and 83.9% specificity) of LUS in diagnosing pneumonia. When including only a consolidation size of >1 cm, the specificity of LUS was higher than CXR (19).

In our cohort, children with a higher LUS score were infected with RSV more often, which is consistent with the results of study by Ghazaly et al., that showed the more severe course of illness caused by RSV compared to other respiratory viruses (20). In line with published literature, our results confirm good concordance of LUS score with illness severity, and adds additional information for management of patients with acute bronchiolitis.

We assessed the usefulness of the LUS score and CAS to identify patients who will require NRS by ROC curve analysis. According to the AUC of the ROC curve, the LUS score would be an insufficiently reliable test to identify patients who will require NRS, as the AUC was <0.8, and the sensitivity and specificity of the delimitation point of >8.5 points were 85% and 58%, respectively. The AUC of the ROC curve for CAS, however, was between 0.9 and 0.8, placing CAS in the realm of good discriminatory tests (21). A similar analysis was done by Bueno-Campaña et al. They analysed the value of LUS to identify patients who would require any form of respiratory support. In their study, the AUC of the LUS ROC curve was 0.845 (CI 95%: 0.78–0.91%), the delimitation sensitivity and specificity were 89.1% and 56% respectively (22). Unfortunately, the sample size in our study was smaller than required for this analysis, making a definitive conclusion inappropriate.

Other studies have found that the LUS score can be used to identify children who will need O_2 therapy (1, 15), which is an indirect indicator of the need for hospitalisation. Since we only included hospitalised infants, the predictive value of the LUS score to identify infants that will need hospitalisation or O_2 therapy was not evaluated in our study.

Limitation of Study

The main limitation of this study is the low sample size. Due to COVID-19 pandemic the inclusion period was short, so we included limited number of patients. Accordingly, some of the differences that are present in the population may not be detected in our study. In addition, no patients required invasive ventilation or met the LUS score criteria for severe bronchiolitis. The concurrent outbreak of the SARS-CoV-2 pandemic unfortunately led to the premature termination of the study, and affected the number of hospitalized children indirectly, since the measures designed to curb the spread of the SARS-CoV-2 pandemic also reduced the spread of other respiratory viral agents in the population, most of which cause acute bronchiolitis in children (23).

Another possible limitation is the influence of subjective assessment of some clinical signs in the CAS score, which was evaluated by different paediatricians at admission. However, all LUS examinations were performed by a single physician, therefore the interpretation was uniform. On the other hand, the examiner was not totally blinded to the clinical picture of individual patients, which could potentially affected interpretation.

The results of our study show that LUS is a good indicator of the severity of acute bronchiolitis in children up to 3 months of age. It suggests that the inclusion of LUS in the management protocol of such patients would contribute to the quality of treatment, and likely reduce the need for CXRs. The value of LUS in detecting complications of acute bronchiolitis has not yet been properly evaluated.

Conclusion

Our research has shown that patients with a higher LUS score had a more severe clinical presentation upon admission and required O_2 therapy for a longer period. Moreover, they were more likely to be infected by RSV and require NRS support. The predictive value of LUS score as a test for identifying patients who will require NRS was not satisfactory. Including LUS in the management protocols of children with acute bronchiolitis could offer additional information to the attending clinicians, and could help in management decisions. More research on a larger number of patients is needed to be able to evaluate the usefulness of LUS reliably in the population of children with bronchiolitis.

Conflict of Interest: The authors declare that they have no conflict of interest.

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