**Abstract:** There is increasing recognition of the role of lung ultrasound (LUS) to assess bronchiolitis severity in children. However, available studies are limited to small, single-center cohorts. We aimed to assess a qualitative and quantitative LUS protocol to evaluate the course of bronchiolitis at diagnosis and during follow-up. This is a prospective, multicenter study. Children with bronchiolitis were stratified according to clinical severity and underwent four LUS evaluations at set intervals. LUS was classified according to four models: (1) positive/negative; (2) main LUS pattern (normal/interstitial/consolidative/mixed) (3) LUS score; (4) LUS score with cutoff. Two hundred and thirty-three children were enrolled. The baseline LUS was significantly associated with bronchiolitis severity, using both the qualitative (positive/negative LUS \( p < 0.001 \)) and quantitative models (cutoff score > 9 \( p < 0.001 \)). Better cut off value was declared at a value of >9 points. Conclusions: Our study supports the role of a comprehensive qualitative and quantitative LUS protocol for the identification of severe cases of bronchiolitis and provides data on the evolution of lung aeration during follow-up.

**Keywords:** bronchiolitis; lung ultrasound; children; respiratory syncytial virus; ultrasound score
1. Introduction

Bronchiolitis is an acute lower respiratory tract infection affecting children under one [1] or two years of age [2], according to the Italian Consensus or to American Academy of Pediatrics (AAP) guidelines. It is the most common cause of non-elective hospitalization in these age groups [3–6]. Diagnostic criteria for bronchiolitis are based on clinical history and examination [1,2,7]. Current guidelines do not suggest to routinely perform laboratory tests and, importantly, chest X-rays should be reserved for the most severe cases [2]. During the last decade, lung ultrasound (LUS) has been proved to be a useful diagnostic tool in many pediatric and neonatal diseases [8–12] and its application and utility in the management of bronchiolitis has also been reported [13–30].

However, available studies are limited by being mainly single-center studies that only assessed LUS scores during initial evaluation, using a limited bundle of LUS signs. Since bronchiolitis is a dynamic disease which may rapidly worsen in hours/days, a prospective longitudinal study addressing the role of LUS performed along multiple time-points is still highly needed. For these reasons, we performed a study aiming to define the prognostic role of LUS in children with bronchiolitis and its role in the short-term follow-up and monitoring of the disease.

2. Patients and Methods

2.1. Population

This is an observational cohort and prospective, longitudinal and analytic study of a multicenter national cohort study, conducted between November 2018 and April 2020 in 12 Italian centers (Supplementary Table S1).

We included children aged 0–12 months with a clinical diagnosis of bronchiolitis. After the first clinical examination, the severity of bronchiolitis was categorized by a severity score, as mild, moderate and severe illness according to Baraldi et al. [1], before the execution of the ultrasound exam.

Exclusion criteria (based on clinical-anamnestic data, not on ultrasound findings), in analogy to the literature [13–30] were applied rigorously to avoid over fitting: children with immunosuppression, heart diseases, pneumonia (when the clinician according to clinical, laboratory and radiologic data classified the child has having pneumonia rather than bronchiolitis), neuromuscular diseases, cystic fibrosis, bronchopulmonary dysplasia (excluded according to the perinatal history, dependence of oxygen), positive history of foreign body inhalation, unstable critical conditions that required immediate life-saving procedures, and lack of parental consent. No control cases were enrolled because the aim of the study was to compare different stages of clinically diagnosed bronchiolitis. An individual data sheet for the collection of demographic, medical and clinical data, according to the clinical classification of bronchiolitis (Table 1), was used.

Table 1. Clinical criteria used to classify bronchiolitis according to Consensus Baraldi et al. (modified). The presence of two or more criteria from each category listed in the table attribute bronchiolitis to that severity class.

| RESPIRATORY RATE | MILD | MODERATE | SEVERE |
|------------------|------|----------|--------|
| Normal or slightly increased | Increased | Significantly increased. |
| RESPIRATORY WORK | Slight retractions of the chest wall | Modest retractions of the chest wall | Significant retractions of the chest wall |
| SATURATION OF OXYGEN | Modesty retractions of the chest wall | Sway of the head (nodding) | Grunting |
| O2 supplementation not required | Breath of the nasal fins | | Breath of the nasal fins |
| SatO2 > 95% | SatO2 90–95% | SatO2 < 90% |
| FEEDING | Normal or slightly reduced | 50–75% of normal food intake | <50% of normal food intake |
| Normal or slightly reduced | | | Inability to feed |
| APNEA | Absent | Brief episodes | Episodes on the rise |

The study was approved by the Tuscan Meyer Committee (n 171/2018) and by the ethics committees of each participating center. For each patient enlisted, written consent was obtained from the parents.
2.2. Lung Ultrasound

LUS was standardized both in terms of examination methods and timing. A 10 MHz (median frequency) linear probe, standard abdominal preset, mechanical index lower than 0.7, intermediate gain to obtain a pleural line defined but not too saturated, unique focus on the pleural line and depth 3–5 cm were used. The acquisitions were achieved by physicians having at least one year experience in pediatric LUS, using fundamental and harmonic images in relation to the technical characteristics of the ultrasound systems used by individual operators and in relation to the experience of the operator themself.

The first ultrasound was carried out within 3–6 h of the first clinical assessment in each participating center. The second, third and fourth ultrasound were performed at 24, 72–96, and 144 h after first LUS.

Eight pulmonary fields were explored in each ultrasound (Figure 1). For each field, longitudinal and transverse scans were made (sixteen ultrasound scans total). Posterior lung fields were divided into paravertebral and basal as suggested in the literature by the studies of Basile and Taveira [14,17].

![Division of Lung Fields for Ultrasound Scans](image_url)

**Figure 1.** Division of lung fields for ultrasound scans. Eight pulmonary fields were explored in each ultrasound. For each field longitudinal and transverse scans were made for a total of sixteen ultrasound scans.

Each step of the clinical and ultrasound evaluation involved the dichotomous attribution (presence or absence) of ultrasound signs compatible with the diagnosis of bronchiolitis, the total grading of each area explored, and the number of involved areas.

In accordance with literature data [31–33], which recognize vertical artifacts and consolidations in the bronchiolitis, the following classification of LUS findings was used: (Figure 2, Supplementary Figure S1).

- **A-lines:** Horizontal reverbs of pleural line, normal ultrasound finding (Score 0 for the quantitative analysis, negative for the dycotomous analyses).
- **Short vertical artifacts (SVA, artifacts that do not reach the bottom of the screen, using a depth setting of 3 cm)** According to a recent hypothesis [34], short artifacts may be produced by small channel or by acoustic traps which allows a quick release of the trapped acoustic energy [33]. Acoustic traps of this type are compatible with simple geometries such as those caused by minimal superficial alveolar collapses. Their microatelectatic nature and easy reversibility, in our opinion, justifies their distinction from the usual artifacts (B-Lines).
- **B-Lines** showing a density of no more than 2 B lines per cm of the pleural line, with a depth setting of 3 cm, were described as Isolated B-Lines. Short vertical artifacts and Isolated B-Lines were considered clinically non-significant findings. Consequently,
they were interpreted negative for dycotomous analyses, but received a score 1 for the quantitative analysis.
- Multiple B lines (Lines B with a distance between them of less than half a cm to the confluence, remaining identifiable from each other) were considered pathological findings (positive), with a quantitative score of 2.
- White lung (Subpleural field with various shades of white/gray without distinguishing lines B), pathological findings (positive), with a quantitative score of 3.

The ultrasound score of each patient was obtained from the sum of the individual scores of each involved area in that patient, considering the worst finding of each area. The logic of this increasing score was based on the physical and anatomical significance of the findings considered, in the hypothesis that each pattern represents an evolutionary degree of loss of lung ventilation from isolated B-Lines to consolidation, through the white lung [31–33].

Finally, the number of affected areas and the involvement of the paravertebral posterior fields were considered for the analysis of multivariate models, in consideration of their possible prognostic role [14].

LUS findings were reported on a model contained in the operator card, in order to reduce the operator variability as much as possible [37].
2.3. Statistical Analysis

Descriptive statistics were expressed as mean ± standard deviation or absolute frequency and percentage, where appropriate. For categorical variables, a univariate analysis was performed by χ² test or the Fisher exact test, where appropriate, and comparisons between different time points were performed by McNemar test. For continuous variables, differences in means were tested by t-test for independent samples in the homoscedastic or the heteroscedastic version depending on the variabilities observed, and follow up comparisons were evaluated by paired samples t-test. Kolmogorov–Smirnov test was used to assess the normality of the data.

To identify the ecographic score cutoff value of 9, a receiver operating characteristic (ROC) curve analysis was performed and the area under the curve (AUC) and its 95% confidence interval (95% CI) was used to evaluate its performance. As the cutoff value was considered the one with the best performance, in term of both sensitivity and specificity, measured by the Youden index.

To quantify the effect of each ecographic pattern on predicting the diagnosis at t0, a logistic regression analysis was performed, and results were expressed by odds ratios (OR) and their 95% CI.

Both univariate and multivariate models were adopted. In univariate models, only the four different ecographic patterns were separately considered. In multivariate models, each ecographic pattern was adjusted by other ecographic patterns. In order to assess the predictive role of baseline LUS on the severity of bronchiolitis, four univariate logistic models and four multivariate logistic models were used. In univariate models, one of the four LUS patterns was considered as the only independent variable, while in multivariate models, in addition to the single LUS models, the number of fields involved, and the involvement of paravertebral fields were added as independent variables.

Multicollinearity was evaluated by the variance inflation factor (VIF) and considered relevant when VIF > 5.

For each model, predicted probabilities for each case were calculated and used in a ROC analysis. AUCs, as well as the sensitivities and specificities of the models and their 95% CI were also evaluated. AUCs were compared by the De Long test, and sensitivity and specificity 95% CIs were determined by the Jeffrey method.

Generalized Estimating Equation (GEE) models accounting for repeated measures were used to evaluate the effect of each ultrasonographic pattern on predicting the severity, considering all the four times observed. Moreover, within the repeated measure analysis, both univariate and multivariate models were adapted.

Given that the number of cases of bronchiolitis treated in the specialized centers depends on the trend of respiratory virus epidemics, in designing the study the sample size was defined on the basis of the expected number of cases in the participating centers in the period of enrollment. In the pre-covid19 era, between 250 and 500 cases were expected to be observed.

Analysis was performed using SPSS Statistics for Windows, Version 23.0 (IBM SPSS, Statistics for Windows, Version 23.0. Armonk, NY, USA: IBM Corp.) and statistical significance was considered as p < 0.05.

3. Results

3.1. Study Population

A total of 233 patients (60.1% males, mean age 109.3 ± 86.1 days) were enrolled (Figure 3). The moderate/severe category were accurate in a single cohort due to the small number of severe forms. 160 (68.7%) had mild, 62 (26.6%) moderate, and 11 (4.7%) severe bronchiolitis. Demographic and clinical details are shown in Table 2.

At the first ultrasound, patients with moderate/severe bronchiolitis had a worse ultrasound compared with those with mild bronchiolitis (Table 3). Children with moderate/severe bronchiolitis more frequently had a positive ultrasound, higher scores or scores higher than the cut-off value of 9, and more fields involved. Conversely, an early involvement of paravertebral areas was more frequent in mild cases.
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Table 2. Study Population. RSV: respiratory syncytial virus. * Home therapy before hospital admission (hypertonic solution and/or Bronchodilators and/or Cortisone for od).

| Characteristics                        | All (n = 233)   | Bronchiolitis Mild (n = 160) | Bronchiolitis Moderate/Severe (n = 73) | $p$ Value |
|----------------------------------------|----------------|-----------------------------|--------------------------------------|-----------|
| Age, days (SD)                         | 109.3 (±86.1) | 122.7 (±92.1)               | 80 (±62.3)                           | 0.001     |
| Sex                                    |                |                             |                                      |           |
| Female, $n$ (%)                        | 93 (39.9%)     | 72 (45%)                    | 21 (28.8%)                           | 0.019     |
| Male, $n$ (%)                          | 140 (60.1%)    | 88 (55%)                    | 52 (71.2%)                           |           |
| Prematurity ($n = 230$)                |                |                             |                                      |           |
| Yes, $n$ (%)                           | 20 (8.7%)      | 11 (7.0%)                   | 9 (12.3%)                            | 0.182     |
| History of difficulty in feeding ($n = 228$) |                |                             |                                      |           |
| Yes, $n$ (%)                           | 151 (66.2%)    | 92 (59.4%)                  | 59 (80.8%)                           | 0.001     |
| * Home therapy before hospital admission for three days ($n = 231$) |                |                             |                                      |           |
| Yes, $n$ (%)                           | 117 (50.6%)    | 85 (53.8%)                  | 32 (43.8%)                           | 0.159     |
| Rhinorrhea ($n = 231$)                 |                |                             |                                      |           |
| Yes, $n$ (%)                           | 227 (98.3%)    | 156 (98.7%)                 | 71 (97.3%)                           | 0.425     |
| Crackling noises on physical examination ($n = 230$) |                |                             |                                      |           |
| Yes, $n$ (%)                           | 198 (86.1)     | 134 (84.8%)                 | 64 (88.9%)                           | 0.407     |
| Wheezing ($n = 230$)                   |                |                             |                                      |           |
| Yes, $n$ (%)                           | 154 (67%)      | 107 (67.7%)                 | 47 (65.3%)                           | 0.715     |
| Fever ($n = 231$)                      |                |                             |                                      |           |
| Yes, $n$ (%)                           | 83 (35.9%)     | 52 (32.9%)                  | 31 (42.5%)                           | 0.159     |
| Intercostal retractions ($n = 231$)    |                |                             |                                      |           |
| Yes, $n$ (%)                           | 164 (71%)      | 96 (60.8%)                  | 68 (93.2%)                           | 0.001     |
| Increased Respiratory Rate ($n = 230$) |                |                             |                                      |           |
| Under 50 breath/min, $n$ (%)           | 75 (32.6%)     | 35 (22.3%)                  | 40 (54.8%)                           | 0.001     |
| Between 51–60 breath/min, $n$ (%)      | 106 (46.1%)    | 95 (60.5%)                  | 11 (15.1%)                           |           |
| Above 61 breath/min                    | 49 (21.3%)     | 27 (17.2%)                  | 22 (30.1%)                           |           |
| Oxygen saturation ($n = 229$)          |                |                             |                                      |           |
| Under 92% in aa, $n$ (%)               | 39 (17%)       | 10 (6.4%)                   | 29 (39.7%)                           | 0.001     |
| Between 93–95% in aa, $n$ (%)          | 45 (19.7%)     | 17 (10.9%)                  | 28 (38.4%)                           |           |
| Above 95% in aa, $n$ (%)               | 145 (63.3%)    | 129 (82.7%)                 | 16 (21.9%)                           |           |
Table 2. Cont.

| LUNG ULTRASOUND MODELS | All (n = 233) | Bronchiolitis Mild (n = 160) | Bronchiolitis Moderate/Severe (n = 73) | p Value |
|-------------------------|--------------|----------------------------|--------------------------------------|-------|
| RSV (n = 216) | | | | |
| Positive, n (%) | 126 (58.3%) | 73 (51.0%) | 53 (72.6%) | 0.002 |
| Chest X-ray (n = 228) | | | | |
| Yes, n (%) | 160 (70.2%) | 29 (18.7%) | 39 (53.4%) | 0.001 |
| Hospitalization | | | | |
| Yes, n (%) | 192 (82.4%) | 119 (74.4%) | 73 (100.0%) | 0.001 |
| HFNC (n = 225) | | | | |
| Yes, n (%) | 50 (22.2%) | 16 (10.5%) | 34 (47.2%) | <0.001 |
| nCPAP (n = 225) | | | | |
| Yes, n (%) | 5 (2.2%) | 0 (0%) | 5 (6.9%) | 0.001 |

Table 3. Results at the baseline lung ultrasound. Comparison of LUS findings between patients with moderate/severe and mild bronchiolitis.

| LUNG ULTRASOUND MODELS | All Cases (n = 233) | Mild Bronchiolitis (n = 160) | Moderate/Severe Bronchiolitis (n = 73) | p Values |
|-------------------------|---------------------|------------------------------|--------------------------------------|-------|
| Ultrasound positive vs. negative | | | | |
| Ultrasound positive, n (%) | 182 (78.1) | 113 (71.9) | 67 (91.8) | 0.001 |
| Ultrasound negative, n (%) | 51 (21.9) | 45 (28.1) | 6 (8.2) | |
| Qualitative result ultrasound | | | | |
| Normal, n (%) | 51 (21.9) | 45 (28.1) | 6 (8.2) | 0.001 |
| Interstitial, n (%) | 17 (7.3) | 14 (8.8) | 3 (4.1) | |
| Consolidative, n (%) | 37 (24.5) | 39 (24.4) | 18 (24.7) | |
| Mixed n (%) | 108 (46.4) | 62 (38.8) | 46 (63) | |
| Score, mean (SD) | 9.4 (5.2) | 7.9 (4.3) | 12.8 (5.6) | 0.001 |
| Score cut off > 9, n (%) | 105 (45.1%) | 49 (30.6%) | 56 (76.7%) | 0.001 |
| Lung fields number, mean (SD) | 2.2 (1.8) | 1.7 (1.6) | 3.3 (1.9) | 0.001 |
| Early involvement of the paravertebral field on LUS | | | | |
| No, n (%) | 80 (34.3%) | 69 (43.1%) | 11 (15.1%) | <0.001 |
| Yes, n (%) | 153 (65.7%) | 91 (56.9%) | 62 (84.9%) | |

3.2. Association between Initial LUS and Bronchiolitis Severity

LUS performed at baseline presentation was significantly associated with the severity of bronchiolitis when both qualitative patterns (positive vs. negative LUS; consolidated vs. normal LUS pattern or mixed vs. normal LUS) and quantitative models (using a cutoff score of 9 by increasing the value of the score) were used (Table 4). Better cut off value was declared a value > 9 points.

The multivariate models (Table 4), in which other LUS patterns have been considered, including the extension of lung disease (number of fields involved) and the early involvement of paravertebral fields, showed that only the quantitative score (OR 4.224; 95% CI 1.590–11.223; p = 0.004) and the extension of involved lung areas (OR 1.615; 95% CI 1.279–2.039; p < 0.0001) were significantly associated with bronchiolitis severity. Moreover, both in the positive/negative ultrasound qualitative models and in the 4-level ultrasound model, the statistically significant OR estimate was close to 1.6, indicating that for each extra lung field involved there was a 60% increase in the risk of moderate/severe bronchiolitis.

The ROC analyses show diagnostic capabilities of the different qualitative and quantitative to predict bronchiolitis severity (Figure 4, Table 5, Supplementary Table S3).

Of the four AUC, although all statistically significant, the two related to qualitative patterns had low accuracy (0.6), having a high sensitivity of 0.918 for the positive/negative result and 0.877 for the 4-level LUS patterns, but low specificities, respectively 0.281 and 0.369. Conversely, the AUC related to the ultrasound score was higher and with values of 0.761 and 0.730, respectively, for the quantitative score and for the dichotomized score (cutoff 9), and showed a better balance between sensitivity, and specificity.
Adding to the ROC analysis the LUS variables “extension” and “early involvement of paravertebral areas” (Figure 3, Supplemental Table S4), the diagnostic ability of the models improved with the AUC that rose to 0.74, indicating greater diagnostic accuracy. For the two models, sensitivity reduction was observed to 0.658 for the positive/negative model and 0.644 for the 4-level model, with a significant increase in specificity rising to 0.725 and 0.731, respectively.

Table 4. Multivariate models showing correlation of the different lung ultrasound models at baseline with bronchiolitis severity.

| Model | Variables in the Model | OR | 95% CI | p Value |
|-------|------------------------|----|--------|---------|
| Univariate models | Positive ultrasound | Yes | 4.370 | 1.770 | 10.785 | 0.001 |
| | No | | 1 | | |
| Ultrasound result | Interstitial | Yes | 1.607 | 0.355 | 7.276 | 0.538 |
| | Consolidative | Yes | 3.462 | 1.290 | 9.366 | 0.017 |
| | Normal | Yes | 5.865 | 2.188 | 14.150 | <0.001 |
| | No | | 1 | | |
| Score | Yes | 1.226 | 1.146 | 1.311 | <0.001 |
| | No | 7.462 | 3.941 | 14.129 | <0.001 |

MULTIVARIATE MODELS BASED ON QUALITATIVE LUS (positive vs. negative) without or with other LUS variables (Early involvement of paravertebral lung fields and extension)

| Model | Variables in the Model | OR | 95% CI | Sensitivity | Specificity | p Value |
|-------|------------------------|----|--------|-------------|-------------|---------|
| Univariate models | Positive ultrasound | Yes | 4.370 | 1.770 | 9.366 | 0.001 |
| | No | | 1 | | |
| Early involvement of paravertebral lung fields | Yes | 1.607 | 0.355 | 7.276 | <0.001 |
| | No | | 1 | | |
| Number of fields involved | Yes | 1.226 | 1.146 | 1.311 | <0.001 |
| | No | 7.462 | 3.941 | 14.129 | <0.001 |

MULTIVARIATE MODELS BASED ON QUALITATIVE LUS (type of lung disease) without or with other LUS variables (Early involvement of paravertebral lung fields and extension)

| Model | Variables in the Model | OR | 95% CI | Sensitivity | Specificity | p Value |
|-------|------------------------|----|--------|-------------|-------------|---------|
| Univariate models | Positive ultrasound | Yes | 4.370 | 1.770 | 9.366 | 0.001 |
| | No | | 1 | | |
| Early involvement of lung fields | Yes | 1.607 | 0.355 | 7.276 | <0.001 |
| | No | | 1 | | |
| Number of fields involved | Yes | 1.226 | 1.146 | 1.311 | <0.001 |
| | No | 7.462 | 3.941 | 14.129 | <0.001 |

MULTIVARIATE MODELS BASED ON QUANTITATIVE LUS (mean score) without or with other LUS variables (Early involvement of paravertebral lung fields and extension)

| Model | Variables in the Model | AUC | p Value | 95% CI | Sensitivity | Specificity | LR + | LR − | 95% CI |
|-------|------------------------|-----|---------|--------|-------------|-------------|------|------|--------|
| Univariate models | Positive ultrasound | 0.600 | 0.015 | 0.52 | 0.67 | 0.918 | 0.838 | 0.965 | 0.281 | 0.216 | 0.354 | 0.3 | 0.1 | 0.7 |
| | Ultrasound 4 level | 0.654 | <0.001 | 0.58 | 0.72 | 0.877 | 0.787 | 0.937 | 0.369 | 0.297 | 0.445 | 1.4 | 1.2 | 1.6 | 0.3 | 0.2 | 0.6 |
| | Score | 0.761 | <0.001 | 0.68 | 0.83 | 0.767 | 0.661 | 0.852 | 0.694 | 0.619 | 0.761 | 2.5 | 1.9 | 3.3 | 0.3 | 0.2 | 0.5 |
| | Score > 9 | 0.738 | <0.001 | 0.66 | 0.80 | 0.658 | 0.544 | 0.759 | 0.725 | 0.652 | 0.790 | 2.4 | 1.8 | 3.2 | 0.5 | 0.3 | 0.7 |
| Multivariate models | Positive ultrasound | 0.743 | <0.001 | 0.67 | 0.81 | 0.644 | 0.530 | 0.746 | 0.731 | 0.659 | 0.795 | 2.4 | 1.8 | 3.3 | 0.5 | 0.4 | 0.7 |
| | Ultrasound 4 level | 0.743 | <0.001 | 0.67 | 0.81 | 0.644 | 0.530 | 0.746 | 0.731 | 0.659 | 0.795 | 2.4 | 1.8 | 3.3 | 0.5 | 0.4 | 0.7 |
| | Score | 0.762 | <0.001 | 0.69 | 0.83 | 0.767 | 0.661 | 0.852 | 0.700 | 0.626 | 0.767 | 2.6 | 2.0 | 3.3 | 0.3 | 0.2 | 0.5 |
| | Score > 9 | 0.795 | <0.001 | 0.68 | 0.82 | 0.767 | 0.661 | 0.852 | 0.694 | 0.619 | 0.761 | 2.5 | 1.9 | 3.3 | 0.3 | 0.2 | 0.5 |

Children with RSV bronchiolitis had statistically significant higher scores. Comparisons between bronchiolitis RSV+/RSV− children are shown in the Supplementary Table S4.

Table 5. ROC Models. Univariate and multivariate models.
Figure 4. ROC curves comparing qualitative (positive/negative LUS, 4-level LUS including normal, interstitial, consolidative and mixed pattern) and quantitative (mean scores, cutoff score of 9) LUS models. ** ROC curves using the LUS models with the adjunction of the LUS variables “extension” and “early involvement of paravertebral areas”.

3.3. Role of LUS in the Monitoring of Bronchiolitis

One hundred and eighty-five (82.9%) were completely followed-up being enrolled at all scheduled controls. Changes of LUS qualitative and quantitative findings are detailed in Table 6 and Figure 5. Overall, LUS results gradually improved over time. In particular, considering the basal time and the last observation, the overall percentage of patients with moderate/severe bronchiolitis had gone from 26.5% to 4.3% ($p < 0.001$), the positive LUS passed from 80% to 53% ($p < 0.001$), the “mixed” result from 47.6% to 18.9% ($p < 0.001$). The percentage of patients with above-threshold scores decreased from 45.9% to 21.6% ($p < 0.001$) as had improved the average score and the average number of fields involved (9.5 to 6.2, $p < 0.001$; and 2.3 to 1.2, $p < 0.001$, respectively).
Table 6. Changes in lung ultrasound (LUS) models during the different subsequent controls (T0, T1, T2 and T3), and changes in treatments offered. HFNC: high flow nasal cannulae. nCPAP: nasal Continuous Positive Airway Pressure.

| LUS PATTERNS | T0 | T1 | T2 | T3 | p Value |
|--------------|----|----|----|----|---------|
| NORMAL       | 35 (20%) | 37 (20%) | 31 (19%) | 26 (16%) | <0.001 |
| INTERSTITIAL | 14 (8%) | 14 (8%) | 15 (9%) | 17 (11%) | 1.0 |
| MIXED        | 46 (27.5%) | 51 (30.2%) | 43 (26.4%) | 40 (25.1%) | 0.1 |

Figure 5. Lung Ultrasound (LUS) patterns at baseline and during follow-up. (A) shows changes in number of children with positive LUS; (B) shows changes in type of patterns; (C) shows changes in mean scores; (D) shows number of children with a LUS score higher than 9.
The univariate and multivariate logistic analyses comparing the different LUS modules at the last control with the severity of bronchiolitis during the same evaluation is shown in Table S5. We found that the qualitative and quantitative scores still significantly correlated with the clinical picture, although the odds ratio was smaller compared to those at baseline (Table 3), supporting the evidence of an overall improvement of LUS findings.

4. Discussion

Our study found that qualitative and quantitative LUS findings are suggestive of an association with bronchiolitis severity and are useful in the follow-up of patients. To our knowledge, this is the largest prospective, multicenter study using a standardized follow-up and a well-established LUS protocol.

Although an association between LUS and bronchiolitis severity was already partially seen in previous studies [13–26], they were monocentric and included relatively small samples. More importantly, they included a combination of artifacts, not in line with recent advances in the field of LUS which highlight the potential of the multiple possible artifacts to be used to provide a semi-quantitative assessment of lung disease [32,33,35,36,38]. A quantitative approach can be more useful for personalized approaches to define disease severity and to quantify the changes of lung disease during follow-up. These aspects have been assessed in neonatal diseases [39], but never studied before in children with bronchiolitis. In our study, we used both quantitative and qualitative models that also included the analyses of different LUS patterns (interstitial, consolidative, mixed or normal), the early involvement of paravertebral areas and the extension of lung disease.

We found that children with moderate/severe bronchiolitis had a higher probability of having a positive LUS, higher scores and more lung areas involved. In addition, we found that the consolidative pattern indicated a three times greater probability of having moderate/severe bronchiolitis than those with a normal ultrasound pattern, and a mixed pattern of a 5-fold increase. The proposed gravity score was validated, as for every single point increase in the score there was an increase of 22.6% the risk of having moderate/severe bronchiolitis.

The ROC analyses allowed us to compare the accuracies of the qualitative and quantitative models. We found that the qualitative LUS models had a low diagnostic accuracy, being the good sensitivity [92%] of ultrasonography penalized by its low specificity. A better performance was achieved by introducing the ultrasound score and cutoff system (sensitivity and specificity of 77% and 69%, respectively). Interestingly, the accuracy of the model improved when we also included the number of thoracic fields involved (the extension of lung involvement), with a 60% increase in the risk of having a moderate/severe bronchiolitis for each further ultrasound field involved. Our findings suggest, therefore, that a comprehensive approach, that consider both the score and the extension, is necessary to provide a proper assessment of lung disease.

This comprehensive qualitative and quantitative approach needed to quantify severity of lung disease in children with bronchiolitis is in line with the pathophysiology of the disease. Childhood bronchiolitis determines structural alterations of the lung periphery due to altered ventilation related to the phenomenon of bronchiolar phlogosis, resulting in air trapping, dysventilation or atelectasis [40]. Since the ultrasound allows a bedside evaluation of the subpleural lung in terms of density, therefore of reduction [absolute or relative] of the quantitative ratio of the airspace and the interstice, it is reasonable to expect a combination of clinical and ultrasound parameters may be useful in clinical practice. In addition, positive associations between ultrasound and clinical aspects of bronchiolitis reinforce the underlying assumptions about the genesis of the artifact signs described in the literature, validating recent evidence [41–44]. In particular, there is increasing agreement that the B-lines are expression of focal areas (acoustic traps) [31] expressed by their density along the pleural line. Specifically, a worsening progression of the peripheral lung parenchyma seems to be characterized by the transitions from sporadic B lines, including short vertical artifacts, to multiple B lines, white lung and consolidations. White lung may be considered high-grade, preconsolidative lung density [35,36]. Therefore, in our opinion the distinction
between white lung and small consolidation (generally surrounded by white lung) is not such as to vary their respective scores. These concepts have been confirmed in adult and are used to guide the alveolar recruitment maneuvers [39,44].

Although previous studies documented a prevalence of LUS findings in posterior paravertebral pulmonary fields [14], in our study the involvement of these areas was not associated with severity. Consolidation and white lung phenomena in the posterior areas can express only a greater tendency to collapse of these areas in subjects that are often placed in supine position, also in consideration of their rapid reversibility that we found during follow-up. In fact, this pattern has also been documented in other lung disease in young children [45].

Our study was the first one defining a standardized follow-up schedule providing information on LUS changes over time during bronchiolitis. The follow-up LUS assessments showed a progressive improvement of qualitative and quantitative LUS findings and a consensual reduction in the number of lung fields involved. This confirmed the general benignity of the disease and reinforces the hypothesis that much of the radiological alterations are supported by alterations of peripheral ventilation rather than to parenchymal phlogosis or alveolar consolidation. These findings can have clinical implications if confirmed on larger studies, since it can be speculated that the lack of rapid reversibility of LUS signs, especially consolidated, can suggest a bacterial overlap. The ultrasound follow-up also allows us to detect any complications of a bronchiolitis which usually has a benign self-limiting course, since if after an apparent clinical/instrumental improvement a worsening of the subject’s condition is observed, the ultrasound can show larger consolidations with tree-like bronchograms that can suggest possible bacterial complications, as suggested in other studies [19,46].

Another peculiarity of our study, compared with previously published ones, is the use of the quantitative score of SVA. As proved by recent literature, ultrasound is a good tool to define superficial pulmonary alterations. These occur with a flow of pattern ranging from isolated vertical artifacts (Lines B) to white lung, and mixed patterns with consolidation. Although SVA have not been widely described in the lung ultrasound literature, their genetic basis can be predictable, essentially representing acoustic traps capable of small vibrational responses [47,48]. We therefore consider it appropriate to consider them as phenomena of minor hypoventilation, easily reversible, and with less weight in the proposed score. In fact, in a previous study we found that healthy newborns, that have still immature lungs, have several SVA that reduce during the following months [49]. Since we documented them as healthy infants, we only counted the SVA for the quantitative score, but were considered as normal in the qualitative one. In subjects with bronchiolitis these phenomena are present in the majority of cases, they are multifocal and in great majority relative to alterations of the ventilation, considered their rapid reversibility.

Our study has limitations. First, the clinician performing LUS was not blinded to the clinical parameters. Second, we did not include parameters to assess and quantify the pleural line abnormalities. Third, the design of this study did not consider the comparison between echo and X-ray imaging, although more than half of the subjects with moderate/severe bronchiolitis underwent chest X-rays. Fourth, only one subject needed intensive care unit hospitalization. Fifth, the severity score used is not consensus based, but it is supported by recent theoretical hypothesis and experimental models [34–36,48,50]. Sixth, due to the emergency scenario related with COVID-19 pandemic and its impact on the circulation of respiratory viruses, the study ended earlier than planned in February 2020, possibly limiting the number of patients with severe bronchiolitis enrolled. Seventh, no control cases were enrolled because the aim of the study was to compare different stages of clinically diagnosed bronchiolitis. Last, a clarification is needed about some LUS features we have considered or described in the methods section. As there is not yet rigorous classification, standardization and interpretation of LUS features, we have tried to be more rigorous as possible by describing as better as possible each LUS feature (e.g., SVA or non-confluent B lines), with the final goal of allowing the same interpretation of each LUS sign by all the study members, which is particularly relevant in the context of a multicenter
national study. Importantly, although some classifications may not be perfect, they are based on decades of clinical and physical studies of the experts of the Italian Academy of Thoracic Ultrasound, which trained in a standardized way all participants of this study. However, our study has several strengths: the number of patients enlisted is higher than the other studies published in the literature so far; it is a multicenter study; the inclusion of ultrasound follow-up until seven days after first enrollment; the introduction of a unique reporting template that allowed experimenters a more univocal interpretation of the LUS features; the ultrasound execution protocol was strictly defined a priori; the comparison between classes of the same disease which allowed to highlight the prognostic role of LUS.

5. Conclusions

In conclusion, our study found that a comprehensive LUS evaluation, which included a qualitative and quantitative assessment of LUS findings and the extension of the involved areas, does not have a strong association with moderate/severe bronchiolitis but it can still provide useful information to the clinician conducting the follow-up and to the management of bronchiolitis. Moreover, this approach allowed us to define the favorable evolution of lung disease in children with an uncomplicated course of bronchiolitis. These findings confirm the utility of LUS in the management of infants with bronchiolitis.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11144233/s1, Figure S1: Schematic classification of artifacts; Table S1: Italian centers participating in the study; Table S2: Definitions of adopted 2 qualitative models and 2 quantitative models score; Table S3: the comparison between the AUC of the 2 qualitative models without and with the other LUS evidences; Table S4: Comparison between bronchiolitis VRS+/-; Table S5: Multivariate analyses correlating LUS and bronchiolitis severity at last follow-up; Table S6: Changes in treatments offered.

Author Contributions: L.G. conceptualized and designed the study, drafted the initial manuscript, and reviewed, and revised the manuscript and writing of the final draft of the manuscript, was responsible for data collection and clinical assessment of the patients. A.A. conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; was responsible for data collection and clinical assessment of the patients. G.S. conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. D.B. was responsible for data collection and clinical assessment of the patients, for critical revision of the first draft of the manuscript, and for critical writing of the final draft of the manuscript. S.S. was responsible for statistical analyses. M.C.S. was responsible for data collection and clinical assessment of the patients, and for critical revision of the first draft of the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Tuscan Hospital Meyer Ethics Committee (n 171/2018).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: Available upon request.

Acknowledgments: Ecobron group: Silvia Marino (15), Cristina De Rose (3), Simona Scatani (5), Maria Alessia Mesturino (5) Manuela Fierabracci (2), Antonella Gucci (2), Tiziana Controzzi (12), Luca Pierantoni (8), Angela Bucicovshi (6), Lucia Di Dio (6), Alexandre Douf (11), Vanina Rognoni (11), Valentina Canocchi (9), Cristiano Ciacci (9), Elisa Morelli (9), Piero Valentini (3), Vita Antonella Di Stefano (7), Marcello Lanari(8), Raffaele Falsaperla (15) Giuseppe Di Cara (10), Flavio Civitelli (9), Riccardo Inchingolo (16), Andrea Smargiassi (16).

Conflicts of Interest: The authors declare no conflict of interest.
References

1. Baraldi, E.; Lanari, M.; Manzoni, P.; Rossi, G.A.; Vandini, S.; Rimini, A.; Romagnoli, C.; Colonna, P.; Biondi, A.; Biban, P.; et al. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. *Ital. J. Pediatr.* 2014, 40, 65. [CrossRef] [PubMed]

2. Ralston, S.L.; Lieberthal, A.S.; Meissner, H.C.; Alverson, B.K.; Baley, J.E.; Gadomski, A.M.; Johnson, D.W.; Light, M.J.; Maraga, N.F.; Mendonca, E.A.; et al. Clinical practice guideline: The diagnosis, management and prevention of bronchiolitis. *Pediatrics* 2014, 134, e1474–e1502. [CrossRef] [PubMed]

3. Meissner, H.C. Viral bronchiolitis in children. *N. Engl. J. Med.* 2016, 374, 62–72. [CrossRef] [PubMed]

4. González Martínez, F.; González Sánchez, M.I.; Rodríguez Fernández, R. Clinical impact of introducing ventilation with high flow oxygen in the treatment of bronchiolitis in a pediatric ward. In *Anales de Pediatría*; Elsevier: Amsterdam, The Netherlands, 2013; Volume 78, pp. 210–215. [CrossRef]

5. Smith, D.K.; Seales, S.; Budzik, C. Respiratory syncytial virus bronchiolitis in children. *Am. Fam. Physician* 2017, 95, 94–99. [PubMed]

6. Vandini, S.; Biagi, C.; Lanari, M. Respiratory syncytial virus: The influence of serotype and genotype variability on clinical course of infection. *Int. J. Mol. Sci.* 2017, 18, 1717. [CrossRef]

7. Ricci, V.; Delgado Nunes, V.; Murphy, M.S.; Cunningham, S. Bronchiolitis in children: Summary of NICE guidance. *BMJ* 2015, 350, 2305. [CrossRef]

8. Copetti, R.; Cattarossi, L. Ultrasound diagnosis of pneumonia in children. *La Radiol. Medica* 2008, 113, 190–198. [CrossRef]

9. Pereda, M.A.; Chavez, M.A.; Hooper-Miele, C.C.; Gilman, R.H.; Steinhoff, M.C.; Ellington, L.E.; Gross, M.; Price, C.; Tielsch, J.M.; Checkley, W. Lung ultrasound for the diagnosis of pneumonia in children: A meta-analysis. *Pediatrics* 2015, 135, 714–722. [CrossRef]

10. Raimondi, F.; Yousef, N.; Migliaro, F.; Capasso, L.; De Luca, D. Point-of-care lung ultrasound in neonatology: Classification into descriptive and functional applications. *Pediatric Res.* 2018, 90, 524–531. [CrossRef]

11. Musolino, A.M.; Supino, M.C.; Buonsenso, D.; Papa, R.E.; Chiurchiu, S.; Magistrelli, A.; Barbieri, M.A.; Raponi, M.; D’Argenio, P.; Villani, A.; et al. Lung ultrasound in the diagnosis and monitoring of 30 children with coronavirus disease 2019. *Pediatr. Pulmonol.* 2021, 56, 1045–1052. [CrossRef]

12. Buonsenso, D.; Tomà, P.; Scateni, S.; Curatola, A.; Morello, R.; Valentini, P.; Ferro, V.; D’Andrea, M.L.; Pirozzi, N.; Musolino, A.M. Lung ultrasound findings in infants with severe acute viral bronchiolitis? *Pediatr. Radiol.* 2020, 50, 1560–1569. [CrossRef] [PubMed]

13. Caiulo, V.A.; Gargani, L.; Caiulo, S.; Fisicaro, A.; Moramarco, F.; Latini, G.; Picano, E. Lung ultrasound in bronchiolitis: Comparison with chest X-ray. *Eur. J. Pediatr.* 2011, 170, 1427–1433. [CrossRef] [PubMed]

14. Basile, V.; Di Mauro, A.; Scalini, E.; Comes, P.; Lofù, I.; Mostert, M.; Tafuri, S.; Manzonia, M.M. Lung ultrasound: A useful tool in diagnosis and management of bronchiolitis. *BMC Pediatr.* 2015, 15, 1–8. [CrossRef] [PubMed]

15. Kader, M.A.; Samra, M.F.A.; Aal, S.M.A.; Shehata, N.; Khalifa, A. The utility of lung ultrasound in evaluation of infants with suspected bronchitis. *Egypt. J. Radiol. Nucl. Med.* 2016, 47, 1057–1064. [CrossRef]

16. Cohen, J.S.; Hughes, N.; Tat, S.; Chamberlain, J.M.; Teach, S.J.; Boniface, K. The utility of Bedside lung ultrasound findings in bronchiolitis. *Pediatr. Emerg. Care*. 2017, 33, 97–100. [CrossRef]

17. Taveira, M.; Yousef, N.; Miatello, J.; Roy, C.; Claude, C.; Boutilier, B.; Dubois, C.; Pierre, A.F.; Tissières, P.; Durand, P. Can a simple lung ultrasound score predict length of ventilation for infants with severe acute viral bronchiolitis? *Arch. Pediatr.* 2018, 25, 112–117. [CrossRef]

18. Zoido Garrote, E.; García Aparicio, C.; Camila Torrez Villarroel, C.; Pedro Vega García, A.; Muniz Fontán, M.; Oulego Erroz, I. Utilidad de la ecografía pulmonar precoz en bronquiolitis aguda leve-moderada: Estudio piloto. *Ann. Pediatr.* 2018, 78, 10–18. [CrossRef]

19. Biagi, C.; Pierantoni, L.; Baldazzi, M.; Greco, L.; Dormi, A.; Dondi, A.; Faldella, G.; Lanari, M. Lung ultrasound for diagnosis of pneumonia in children with acute bronchiolitis. *BMC Pulm. Med.* 2018, 18, 1–10. [CrossRef]

20. Buonsenso, D.; Supino, M.C.; Giglioni, E.; Battaglia, M.; Mesturino, A.; Scateni, S.; Scialanga, B.; Reale, A.; Musolino, A.M. Point of care diaphragm ultrasound in pediatric community-acquired pneumonia requiring surgical procedures: A two-center prospective study. *Pediatr. Radiol.* 2020, 50, 1560–1569. [CrossRef] [PubMed]

21. Basile, V.; Di Mauro, A.; Scalini, E.; Comes, P.; Lofù, I.; Mostert, M.; Tafuri, S.; Manzonia, M.M. Lung ultrasound: A useful tool in diagnosis and management of bronchiolitis. *BMC Pediatr.* 2015, 15, 1–8. [CrossRef] [PubMed]

22. Kader, M.A.; Samra, M.F.A.; Aal, S.M.A.; Shehata, N.; Khalifa, A. The utility of lung ultrasound in evaluation of infants with suspected bronchitis. *Egypt. J. Radiol. Nucl. Med.* 2016, 47, 1057–1064. [CrossRef]

23. Cohen, J.S.; Hughes, N.; Tat, S.; Chamberlain, J.M.; Teach, S.J.; Boniface, K. The utility of Bedside lung ultrasound findings in bronchiolitis. *Pediatr. Emerg. Care*. 2017, 33, 97–100. [CrossRef]

24. Bueno, M.; Sainz, T.; Alba, M.; Del Rosal, T.; Mendez-Echevarria, A.; Echevarria, R.; Tagarro, A.; Ruperez-Lucas, M.; Herreros, M.L.; Latorre, L.; et al. Lung ultrasound for prediction of respiratory support in infants with acute bronchiolitis: A cohort study. *Pediatr. Pulmonol.* 2019, 54, 873–880. [CrossRef] [PubMed]

25. Özkaya, A.K.; Yılmaz, H.L.; Kendir, Ö.T.; Gökay, S.S.; Eyüboğlu, I. Lung ultrasound findings and bronchiolitis ultrasound score for predicting hospital admission in children with acute bronchiolitis. *Pediatr. Emerg. Care* 2018, 36, e135–e142. [CrossRef] [PubMed]

26. Supino, M.C.; Buonsenso, D.; Scateni, S.; Scialanga, B.; Mesturino, M.A.; Bock, C.; Chiaretti, A.; Giglioni, E.; Reale, A.; Musolino, A.M. Point-of-care lung ultrasound in infants with bronchiolitis in the pediatric emergency department: A prospective study. *Eur. J. Pediatr.* 2019, 178, 623–632. [CrossRef] [PubMed]

27. Ingelse, S.A.; Pisani, L.; Westdorp, M.H.A.; Almakdase, M.; Schultz, M.J.; Wensel, J.B.M.; Bem, R.A. Lung ultrasound scoring in invasive mechanically ventilated children with severe bronchiolitis. *Pediatr. Pulmonol.* 2020, 55, 2799–2805. [CrossRef] [PubMed]
26. Ruiz, N.S.S.; Albarrán, I.R.; Gorostiza, I.; Laka, I.G.; Lejonagoitia, C.D.; Samson, F. Point-of-care lung ultrasound in children with bronchiolitis in a pediatric emergency department. Arch. Pediatrie 2020, 28, 64–68. [CrossRef] [PubMed]

27. Varshney, T.; Mok, E.; Shapiro, A.J.; Li, P.; Dubrovsky, A.S. Point-of-care lung ultrasound in young children with respiratory tract infections and wheeze. Emerg. Med. J. 2016, 33, 609–610. [CrossRef]

28. Di Mauro, A.; Ammirabile, A.; Quercia, M.; Panza, R.; Capezza, M.; Manzionna, M.M.; Laforgia, N. Acute Bronchiolitis: Is there a role for lung ultrasound? Diagnostics 2019, 9, 172. [CrossRef]

29. Jaworska, J.; Komorowska-Piotrowska, A.; Pomięciec, A.; Wiśniowski, J.; Woźniak, M.; Littwin, B.; Kryger, M.; Kwaśniewicz, P.; Szczyrski, J.; Külitiska-Szukalska, K.; et al. Consensus on the application of lung ultrasound in pneumonia and bronchiolitis in children. Diagnostics 2020, 10, 935. [CrossRef]

30. La Regina, D.P.; Bloise, S.; Pepino, D.; Iovine, E.; Laudisa, M.; Cristiani, L.; Nicolai, A.; Nenna, R.; Mancino, E.; Di Mattia, G.; et al. Lung ultrasound in bronchiolitis. Pediatr. Pulmonol. 2020, 56, 234–239. [CrossRef]

31. Soldati, G.; Demi, M.; Smargiassi, A.; Inchingolo, R.; Demi, L. The role of ultrasound lung artifacts in the diagnosis of respiratory diseases. Expert Rev. Respir. Med. 2019, 13, 163–172. [CrossRef]

32. Soldati, G.; Smargiassi, A.; Inchingolo, R.; Sher, S.; Nenna, R.; Valente, S.; Inchingolo, C.D.; Corbo, G.M. Lung ultrasonography may provide an indirect estimation of lung porosity and airspace geometry. Respiration 2014, 88, 458–468. [CrossRef]

33. Soldati, G.; Smargiassi, A.; Demi, L.; Inchingolo, R. Artifactual lung ultrasonography: It is a matter of traps, order, and disorder. Appl. Sci. 2020, 10, 1570. [CrossRef]

34. Demi, M.; Buda, N.; Soldati, G. Vertical artifacts in Lung Ultrasonography: Some common clinician questions and the related engineer answers. Diagnostics 2022, 12, 215. [CrossRef] [PubMed]

35. Soldati, G.; Demi, M.; Inchingolo, R.; Smargiassi, A.; Demi, L. On the physical basis of Pulmonary Sonographic Interstitial Syndrome. J. Ultrason. Med. 2016, 35, 2075–2086. [CrossRef] [PubMed]

36. Demi, M.; Prediletto, R.; Soldati, G.; Demi, L. Physical Mechanisms Providing Clinical Information from Ultrasonound Lung Images: Hypotheses and Early Confirmations. IEEE Trans. Ultrason. Ferroelectr. Freq. Control. 2019, 67, 612–623. [CrossRef]

37. Amendolea, A.; Gori, L.; Adamoli, P.; Limoli, G.; Supino, M.C.; Coco, A.D.; Trobia, G.L.; Tursi, F.; Soldati, G.; Buonconsenso, D. Pleuropulmonary ultrasound in pediatrics. J. Ultrasound Med. 2022. [CrossRef]

38. Volpicelli, G.; Elbarbary, M.; Blaivas, M.; Lichtenstein, D.A.; Mathis, G.; Kirkpatrick, A.W.; Melniker, L.; Gargani, L.; Noble, V.E.; Via, G.; et al. International Liaison Committee on Lung Ultrasonography (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). Intensiv. Care Med. 2012, 38, 577–591. [CrossRef]

39. De Luca, D. The Promise of Lung Ultrasound to Monitor Evolution of Chronic Respiratory Morbidity in Preterm Infants. Chest 2021, 160, 799–800. [CrossRef]

40. Colby, T.V. Bronchiolitis: Pathologic considerations. Am. J. Clin. Pathol. 1998, 109, 101–109. [CrossRef]

41. Mento, F.; Soldati, G.; Prediletto, R.; Demi, M.; Demi, L. Quantitative Lung Ultrasound Spectroscopy Applied to the Diagnosis of Pulmonary Fibrosis: The First Clinical Study. IEEE Trans. Ultrason. Ferroelectr. Freq. Control. 2020, 67, 2265–2273. [CrossRef]

42. Mongodi, S.; De Luca, D.; Colombo, A.; Stella, A.; Santangelo, E.; Corradi, F.; Gargani, L.; Rovida, S.; Volpicelli, G.; Bouhemad, B.; et al. Quantitative Lung Ultrasound: Technical Aspects and Clinical Applications. Anesthesiology 2021, 134, 949–965. [CrossRef] [PubMed]

43. Soummer, A.; Perbet, S.; Brisson, H.; Arbelot, C.; Constantin, J.-M.; Lu, Q.; Rouby, J.-J. Lung aeration loss during a successful weaning trial predicts postextubation distress. Crit. Care Med. 2012, 40, 2064–2072. [CrossRef] [PubMed]

44. Rouby, J.-J.; Arbelot, C.; Brisson, H.; Lu, Q.; Bouhemad, B. Measurement of alveolar recruitment at the bedside: The be-ginning of a new era in respiratory monitoring? Respir. Care 2013, 58, 539–542. [CrossRef] [PubMed]

45. Buonconsenso, D.; Tomà, P.; Pirozzi, N.; Mesturino, A.; Morello, R.; Curatola, A.; Valenti, P.; Dubinsky, T.J.; Musolino, A.M. Lung Ultrasonography in Infants With Respiratory Infections: More Important the Age or the Pathogen? Ultrasound Q. 2020, 36, 118–122. [CrossRef]

46. Buonconsenso, D.; Musolino, A.; Ferro, V.; De Rose, C.; Morello, R.; Ventola, C.; Liotti, F.M.; De Sanctis, R.; Ciaretti, A.; Biasucci, D.G.; et al. Role of lung ultrasound for the etiological diagnosis of acute lower respiratory tract infection (ALRTI) in children: A prospective study. J. Ultrason. 2021, 25, 185–197. [CrossRef]

47. Soldati, G.; Inchingolo, R.; Smargiassi, A.; Sher, S.; Nenna, R.; Inchingolo, C.D.; Valente, S. Ex vivo lung sonography: Morphologic- ultrasound relationship. Ultrasound Med. Biol. 2012, 38, 1169–1179. [CrossRef]

48. Demi, L.; van Hoeve, W.; van Sloun, R.J.G.; Soldati, G.; Demi, M. Determination of a potential quantitative measure-of the state of the lung using lung ultrasound spectroscopy. Sci. Rep. 2017, 7, 12746. [CrossRef]

49. Buonconsenso, D.; Soldati, G.; Curatola, A.; Morello, R.; De Rose, C.; Vacca, M.E.; Lazzareschi, I.; Musolino, A.M.; Valenti, P. Lung Ultrasonography Pattern in Healthy Infants During the First 6 Months of Life. J. Ultrason. Med. 2020, 39, 2379–2388. [CrossRef]

50. Demi, M. The impact of multiple concurrent factors on the length of the ultrasound pulmonary vertical artifacts as illustrated through the experimental and numerical analysis of simple models. J. Acoust. Soc. Am. 2021, 150, 2106–2115. [CrossRef]