The lung ultrasound in children with SARS-COV 2 infection: a national multicenter prospective study

Maria Supino[1], Danilo Buonsenso[2], Rino Agostiniani[3], Laura Gori[4], Vincenzo Tipo[5], Rosa Morello[2], Angelo Giovanni Delmonaco[6], Raffaele Falsaperla[7], Carlotta Biagi[8], Salvatore Cazzato[9], Alberto Villani[1], Anna Maria Musolino[1], Simona Scateni[1], Valentina Ferro[1], Barbara Scialanga[1], Alessia Mesturino[1], Elena Boccuzzi[1], Carolina D'Anna[5], Vittorio Romagnoli[9], Silvia Marino[7], Roberta Puxeddu[3], Gaia Martelli[9], Thaililja Gagliardo[5], Manuel Murciano[1], and Federica Pellizzoni[10]

[1]Ospedale Pediatrico Bambino Gesu
[2]Policlinico Universitario Agostino Gemelli Dipartimento Scienze della Salute della Donna e del Bambino
[3]Azienda USL Toscana centro Sede di Pistoia
[4]Ospedale Santa Chiara
[5]Azienda Ospedaliera di Rilievo Nazionale Santobono Pausilipon
[6]Azienda Ospedaliero Universitaria Citta della Salute e della Scienza di Torino
[7]Azienda Sanitaria Provinciale di Catania
[8]Azienda Ospedaliero Universitaria Ospedali Riuniti di Ancona Umberto I G M Lancisi G Salesi
[9]IRCCS Azienda Ospedaliero-Universitaria di Bologna
[10]Universita Vita Salute San Raffaele

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Abstract

Covid-19 causedhospitalizations, severe disease and deaths in any age, including in the youngest children. The aim of this multicenter national study is to characterize the clinical and the prognostic role of lung ultrasound (LUS) in children with Covid-19. We enrolled children between 1 month and 18 years of age diagnosed with SARS-CoV2 infection and whounderwenta lung ultrasound within 6 hours from firstmedical evaluation. A total of 213 children were enrolled, 51.6%were male, median age was2 years and 5 months (IQR 4mm- 11 yearsand4 months).One hundred and fortyeight (69.4%) children were admitted in hospital, 9 (6.1%) in pediatric intensive care unit.We found an inverse correlation between the LUS score and the oxygen saturationatthe clinical evaluation (r = -0.16; p = 0.019). Moreover, LUS scores were significantly higher in patients requiring oxygen supplementation (8 (IQR 3 - 19) vs 2 (IQR 0 - 4); p= 0.001). Among LUS pathological findings, irregular pleural line, sub-pleural consolidations and pleural effusions were significantly more frequentin patients whoneeded oxygen supplementation (p = 0.007; p = 0.006 andp = 0.001, respectively). This multicentric study confirmed that LUS is able to detect Covid-19 low respiratory tract involvement, which is characterized by pleural line irregularities, vertical artifacts and subpleural consolidations. Notably, children with higher LUS score have an higher risk of hospitalization or need for oxygen supplementation, supporting LUS as a valid and safe point-of-care first level tool for the clinical evaluation of children with Covid-19.

TITLE PAGE

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Maria Chiara Supino[1*], MD, Danilo Buonsenso[2,3], MD, PhD, Rino Agostiniani[4], MD, Laura Gori[5], MD, Vincenzo Tipo[6], MD, Rosa Morello[2], MD, Giovanni Del Monaco[7], MD, Raffaele Falsaperla[8], MD, Carlotta Biagi[9], MD, Salvatore Cazzato[10], MD, Alberto Villani[1], MD, PhD, Anna Maria Musolino[1], MD and the PLUSCOVID-19 Study Group

PLUSCOVID-19 Study group: Pediatric Lung UltraSoundCOrona Virus Disease 19

Simona Scateni[1], MD, Valentina Ferro[1], MD, Barbara Scialanga[1], MD, Maria Alessia Mesturino[1], MD, Elena Boccuzzi[1], MD, Carolina D'Anna[6], MD, Vittorio Romagnoli[10], MD, Silvia Marino[11], MD, Roberta Puxeddu[4], MD, Gaia Martelli[10], MD, Thaililja Gagliardo[6] , MD, Manuel Murciano[1], MD, Federica Pellizzoni[12], MD

Affiliations:

1 Pediatric Emergency Unit, Department of Emergency and General Pediatrics, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy.

2 Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome Italy.

3 Centro di Salute Globale, Università Cattolica del Sacro Cuore, Roma, Italy.

4 Department of Pediatrics, San Jacopo Hospital, Pistoia, Italy.

5 Department of Maternal and Child Health, Division of Pediatric Unit, S. Chiara Hospital, Pisa, Italy.

6 Pediatric Emergency and Short Stay Unit, Santobono-Pausilipon Children's Hospital, Naples, Italy.

7 Pediatric Emergency Unit, City of Health and Science of Turin, Turin, Italy.

8 Neonatal Intensive Care Unit [NICU], AOU "Rodolico-San Marco", PO "San Marco", University of Catania, Catania, Italy.

9 Pediatric Unit, Department of Mother and Child Health, Salesi Children's Hospital, Ancona, Italy.

10 Pediatric Emergency Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.

11 Pediatric and Pediatric Emergency Department, AOUP "Rodolico San Marco", PO "San Marco", University of Catania, Catania

12 Pediatric and Neonatal Unit, San Raffaele Hospital, Università Vita-Salute San Raffaele, Milano

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*** Correspondence:** Maria Chiara Supino, MD

ORCID: https://orcid.org/0000-0003-2507-8886

Pediatric Emergency Unit

Department of Emergency and General Pediatrics

Bambino Gesù Children's Hospital, IRCCS

Piazza Sant'Onofrio 4, Rome, Italy.

Tel: +39 0668592909

E-mail:*mariachiarasupino@gmail.com*

Running title:The lung ultrasound in children with SARS-COV 2 ABSTRACT

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We enrolled children between 1 month and 18 years of age diagnosed with SARS-CoV2 infection and whounderwenta lung ultrasound within 6 hours from firstmedical evaluation.

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This multicentric study confirmed that LUS is able to detect Covid-19 low respiratory tract involvement, which is characterized by pleural line irregularities, vertical artifacts and subpleural consolidations. Notably, children with higher LUS score have an higher risk of hospitalization or need for oxygen supplementation, supporting LUS as a valid and safe point-of-care first level tool for the clinical evaluation of children with Covid-19.

INTRODUCTION

More than two years after the description of the first Covid-19 cases, our understanding of the clinical impact of SARS-CoV-2 on child health is significantly improved. Overall, Covid-19 has caused much higher morbidity and mortality on adults compared with children, although hospitalizations, severe disease and deaths have been recorded in any age, including in the youngest children.[1,2] Moreover, children have also suffered from post-acute complications of SARS-CoV-2 infection, including the Multisystem Inflammatory Syndrome and Long Covid.[3-6]

The recognition that the large majority of children infected with SARS-CoV-2 develop only mild symptoms and spontaneously completely recover poses the challenge to understand the optimal way to specifically evaluateinfected children, rather than simply translating adult practice into pediatrics. For example, symptomatic adults assessed in the emergency department (ED) frequently undergo laboratory diagnostics and imaging, including chest X-Ray or Computed Tomography.[7] This approach was usually routine practice in the pre-vaccine era, when the clinical impact of Covid-19 on adults has been massive, and is now mostly reserved to symptomatic patients. In children, such an approach does not seem justified. As most children have a low risk of develop severe disease and vaccinations further reduce this risk, an approach based on routine traditional imaging does not seem justified, as it is associated with radiation exposure and longer waiting times in the pediatric emergency department (PED).[1]

In this context, an approach based on safe and rapid point-of-care tools to evaluate a child with SARS-CoV-2 infection seems to be more appropriate. As Covid-19 pneumonia mainly affects the peripheral areas of the lungs, early preliminary studies in both adults and children have documented that Lung Ultrasound (LUS) can easily detect low respiratory tract infection (LRTI) during SARS-CoV-2.[8] However, while several adult studies on large cohorts have documented also a prognostic role of LUS in predicting hospitalizations and severe outcomes in infected adults, pediatric studies have provided less conclusive information, as they mostly included a small number of patients from single centers and without enough patients with moderate/severe disease. [9-18]For these reasons, we performed this multicenter national study in order to better characterize the clinical and prognostic role of LUS in children with Covid-19 assessed in the PED.

MATERIALS ANDMETHODS

Study design and population

This national multicenterprospective study was conducted between 15st November 2020 and 30st June 2021 in 8italian hospitals (Bambino GesuChildren Hospital of Rome, A. Gemelli University Polyclinic Foundation of Rome, Santobono-Pausilipon Children's Hospital of Naples, Sant'Orsola Hospital of Bologna, San Jacopo Hospital of Pistoia,Salesi Children's Hospital of Ancona,San Marco Hospital of Catania,City of Health and Science of Turin). After the initial approval by theethics committee of the Bambino Gesu Children Hospital (2293_OPBG_2020), all participating sites obtained approval from their local ethics committee.Written informed consent to participate in this study was provided by the children' legal guardian/next of kin.

We included children with more than 1 month and less than 18 years, withdiagnosis of SARS-CoV2 infection made using molecular o antigenic tests on a nasopharyngeal swab. In all enrolled patients a lung ultrasound was performedwithin 6 hours from the initial medical evaluation. Were excluded patients outside our age range, who refused to participate, severe conditions requiring immediate life-saving procedures, cardiac abnormalities, previous major thoracic surgery, congenital pulmonary malformations, serious malformations of the rib cage, cystic fibrosis, neuromuscular diseases or bronchopulmonary dysplasia.

Lung ultrasound

LUS was performed using an ultrasound machine with a linear probe (10mHzmedian frequency) with a unique focus on the pleural line and a depth of 5 cm. The acquisitions were achieved by physicians having at least one year experience in pediatric LUS.Images and clips were stored and archived.

As suggested by Soldati et aleach hemithorax was divided in 7 areas:3 posterior (superior, inferior and paravertebral), 2 lateral (superior and inferior) and 2 anterior(superior and inferior).[19]

We evaluated the presence of pleural irregularities, subpleural consolidations, B-lines and pleural effusions. The lung pattern was classified in: score 0—normal sliding, a regular pleural line and A-lines with fewer than 2 B-lines; score 1—a pleural line indented with multiple well-defined B-lines; score 2—a broken pleural line associated with dark areas and consolidation areas; score 3—large and multiple patches of white lung. To investigate lung fields the patients were positioned in sitting position. Therefore, we summarized the lung ultrasound score in each area.

Data collection and statistical analysis

Data were collected through a RedCap (Research Electronic Data Capture) program. Each site was identified with a number and the data of individual patients were entered anonymously.The clinical report form collected data on: gender, age, vital signs, diagnostic test performed at arrived (blood sample, chest X-ray, CT scan), signs orsymptoms (e.g. fever, diarrhea, chest pain, dyspnea),type of oxygen therapy during hospitalization and disposition (discharge, admission to ward, pediatric intensive care unit).The LUS report form collected data on presence/absence of short vertical artifacts, isolated or multiple B lines, white lung, consolidation $<$ 1 cm or $>$1 cm, thickening of the pleural line, pleural effusion.Statistical analysis was performed using the SPSS software (IBM SPSS Statistics, version 24.0, Chicago, IL, USA).We tested the normality by Kolmogorov-Smirnovtest. The continuous variables were reported as the mean +- standard deviation (SD) or the median and interquartile range (IQR), as appropriate. Frequencies and percentages (%) were used to describe categorical variables.The Mann–Whitney test andStudent'sttest were used to compare nonparametric and normaldata, respectively, while Pearson's $\chi 2$ test or a Fisher's exact test were used, as appropriate. A p-valueinferior0.05 wasconsideredstatisticallysignificant.

RESULTS

Study population

Two hundred and thirteen patients whit SARS-CoV2 infectionwere enrolledbetween 15st November 2020 and 30st June 2021. One hundred and ten (51.6%) patients were male witha median age of 2 years and 5

months (IQR 4mm- 11 yyand4 mm). Eighty-seven (40.9%) children had less than 1 years of age, of whom 63 (29.6%) had less than 6 months of age. At medical history 160 (75.1%) children presented fever at home, 67 (31.5%)had respiratory symptoms, 75 (35.2%) reported a reductionoffood intake and 106 (49.8%) indicated anepidemiological link. Fifteen (7%) children had chest pain, 8 (3.7%) had anosmia and 6 (2.8%) had ageusia. At clinical evaluation the mean oxygen saturation was 98.4 % (± 2.0) in room air, 16 (7.5%) presented respiratory distressand16 (7.5%) had whistles/wheezingat the auscultation of the thorax. One hundred and forty-eight (69.4%) children were admitted in hospital, of whom 9 (6.1%) in pediatric intensive care unit.Thirteen (6.1%) children needed oxygen therapy during the hospitalization. At LUS examination the median score was of 2 (IQR 0- 5.5). In particular the most encountered ultrasound pathological features are the irregularity of pleural line (33,3%) and the B lines (46.5%). Table 1 summarizes demographic, clinical and LUS findings of children with COVID-19.

Dividing the sample into 2 age groups, greater or less than one years old, we got 2 groups of 87 and 126 children. In Table 2, the demographic, clinical and LUS findings of the two groups are summarized and compared

From a clinical viewpoint, younger children presented a higher rate of reduction of food intake (80.4% *vs* 16.7%; p = 0.001) and a higher rate offever (83.9%*vs* 68.3%; p = 0.009)compared with older patients. We also observed in children whit less of 1 year of age a higher level of oxygen saturationduring the evaluation (99 (+- 1.6)*vs* 98.1 (+- 2.1); p= 0.001) and a lowerneed foroxygen therapy during the hospitalization (0 *vs* 10.3%; p= 0.002)than inolder patients.

Considering LUS pathological features, we observed that the occurrence of the irregular pleural line and the presence of B-lines were seen more frequently in younger children (43% *vs* 60.71%; p = 0.035 and 53.2% *vs* 36.8%; p = 0.013 respectively). Moreover, the presence of sub-pleural consolidation and pleural effusion were significantly more common in children whit greater of 1 year of age (21.4% *vs*5.7%; p= 0.001 and 19.8% *vs* 6.9%; p= 0.006).

No other significant differenceswere evidencedbetween these two groups.

We found an inverse correlation between the LUS score and the oxygen saturation during the clinical evaluation (r = -0.16; p = 0.019).

We also divided the enrolled children in two sample on the basis of the need for oxygen therapy during hospitalization. We summarized in Table 3 the demographic, clinical and LUS findings of the two groups.

We found that the 13 children who needed oxygen therapy were significantly older (13 yy 9 mm (11 yy 7 mm- 16 yy 6 mm) *vs* 1 yy 6 mm (4 mm- 9 yy 8 mm); p= 0.001) and reported more frequently chest pain (30.8% *vs* 5.5%; p= 0.008) than the other group.

Moreover, childrenwho had needed oxygen therapy presented,during the clinical assessment, a lower oxygen saturation (94.3 (+- 3.2) *vs*98.7 (+- 1.5); p= 0.023) and a more frequent hospitalization in intensive care unit (30% *vs* 6.1%; p= 0.017).

Among LUS pathological features, irregular pleural line, sub-pleural consolidation and pleural effusion were significantly greater in who had needed oxygen therapy (69.2% *vs* 31%; p = 0.007;46.2% *vs*13%; p = 0.006 and 53.8%*vs* 12%; p = 0.001, respectively). Finally, the LUS scores were significantly higher in who had needed oxygen therapy (8 (3 - 19) vs 2 (0 - 4); p= 0.001, Figure 1).

We also divided our cohorts in children younger than 5 years, 5-11 years and older than 12 years of age (which reflects the different age groups that have had access to vaccination).

We found that with increasing age decreased the oxygen saturation value found at the time of LUS (p= 0.002) so older patients were those who most frequently needed oxygen therapy (p= 0.001) and hospitalization in intensive care unit (p = 0.001). At LUS older patients had more irregular pleural line and B-Lines than younger children (p = 0.001 and p=0034,respectively). In Table 4, the demographic, clinical and LUS findings of the three groups are summarized.

DISCUSSION

To our knowledge, this is the first multicenter national study assessing LUS findings and their prognostic role in a relatively large cohort of children with microbiologically confirmed SARS-CoV-2 infection. Overall, we found that children with higher LUS scores and with subpleural consolidations have a significantly higher risk of being hospitalized or require oxygen support after initial assessment in the PED.

Our study confirms, on a larger populations, what initially suggested by smaller pediatric cohorts from Italy, Turkey and Spain, showing that children with LRTI during SARS-CoV-2 infection can have a cohort of LUS findings such as vertical artifacts and subpleural consolidations.[13-22] Authors from four different hospitals in Italy, in particular, found vertical artifacts and subpleural consolidations to be the most common findings, while pleural effusions were more rare and more described in children with MIS-C. However, cohorts were mostly limited to less than 50 patients. In general, these LUS artifacts are in line with what we have learnt from the past decade of LUS practice in pediatrics. Although the initial role of LUS has mostly been detecting pneumonia in children, its role has significantly evolved. [8] The better understanding of different semeiotic LUS patterns and of their physical mechanismsled authors to investigate if specific LUS patterns may better discriminate different lung conditions. [23] For example, pediatricians from Rome found LUS patterns (like large consolidations, complicated effusions, fix or liquid bronchograms) as more predictive of bacterial or more severe pneumonia. [24, 25]Similarly, two independent teams investigated if some LUS patterns may be more associated to viral or bacterial pneumonia, both finding that small subpleural consolidations and vertical artifacts are more frequent in viral LRTIs, while large consolidations with bronchograms more in bacterial etiologies. [26, 27] Therefore, our findings that vertical artifacts and small subpleural consolidations are more frequent in Covid-19 pneumonia is in line with what expected from previous LUS literature in adults with Covid-19 or children with other viral conditions. [8]

Our multicenter study allowed us to include a larger number of patients and provide information about prediction of severity, but also subanalyses according to age groups. Unsurprisingly, our study found that children with higher LUS scores of subpleural consolidations had a higher risks of needing hospitalization or oxygen support. These findings are in line with a few pediatric studies which included very small number of children with severe disease, but also confirm studies from adults with Covid-19.[13-19] In adults, several studies have documented how LUS performed in the ED can predict hospitalization, ventilation support and deaths.[10-12]Our findings are not unexpected in light of recent understanding of the physical bases of LUS. [23] In particular, there is growing agreement in literature that vertical artifacts represent peripheral lung abnormalities that generate acoustic traps, eventually seen as vertical lines on LUS. As these abnormalities represent areas of dysventilation and possibly altered gas exchange, it is not unsurprising that those children with more abnormalities on LUS may have a higher risk of developing more severe disease. Similar evidence is already available from other pediatric respiratory conditions like acute bronchiolitis, where several studies have documented that children with higher LUS score have a higher risk of hospitalization, respiratory support and intensive care unit admission.[28]

In our study, we performed subanalyses according to age groups. In general, we found that lung involvement was more significant in children older than 1 year of age, which is in line with a well-established although not yet fully understood gradient of more severe disease according to increasing age.[1] Some authors have suggested that better innate immunity in the upper airways might have contributed to lesser degree of LRTIs in children. [29]In our cohort, children younger than 1 year of age had, in fact, less frequently vertical artifacts and subpleural consolidations, supporting this hypothesis. However, this age groups may also have been protected by maternal antibodies, since maternal vaccinations have started during the study period, although we did not collect this information.[30] Conversely, when we divided our cohorts in children younger than 5 years, 5-11 and older than 12 years of age (which reflects the different age groups that have had access to vaccination), the characteristics of LUS patterns were similar, suggesting that children younger than 5 years of age have a similar rate of LRTI involvement than older one. These data may have clinical implications, as can provide further information to both healthcare workers and parents about the decision of vaccinating or not younger children, a still debated topic.[31]

Our study has limitations to address. The most important limit is the low number of children with critical Covid-19 that required mechanical ventilation. However, such a severe outcome is very rare and would require significantly larger populations, a limit difficult to overcome, even with multicenter studies. Also, our study did not include populations at higher risk of more severe Covid-19, including children with comorbidities, black and latino communities, therefore our findings may not be generalized to different epidemiological contexts. Also, these data refer to pre-omicro era, and therefore more studies are needed understand the impact of LUS in these cohorts. Last, we did not included a cohort of vaccinated children, therefore we have not been able to evaluate the impact of vaccination on the development of LRTI during Covid-19 in children.

In conclusion, this national study on children with Covid-19 confirmed that LUS is able to detect Covid-19 low respiratory tract involvement, which is characterized by pleural line irregularities, vertical artifacts and subpleural consolidations. Importantly, children with higher LUS score have a higher risk of required hospitalization or oxygen support, further supporting LUS a valid and safe point-of-care first level tool for the assessment of children with Covid-19. Further studies will be needed to understand how vaccinations and new variants may determine a different degree of LRTI in children with Covid-19.

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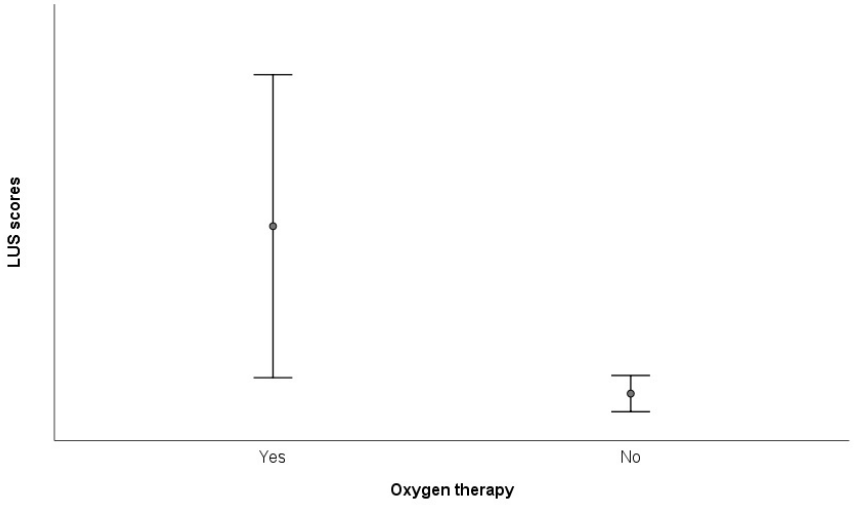

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