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Lung ultrasound features of children with complicated and noncomplicated community acquired pneumonia: A prospective study

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Abstract

Objective: The purpose of this study was to describe lung ultrasound (LUS) findings at baseline and 48 hours after the beginning of treatment and evaluate how they correlate with outcome

Design: We prospectively analyzed patients from 1 month to 17 years of age with community acquired pneumonia (CAP) evaluated at a tertiary level pediatric hospital. At baseline and 48 hours after the beginning of treatment, history, clinical examination, laboratory testing, chest X-ray, and LUS were performed.

Results: One hundred one children were enrolled in the study (13 with complicated CAP). At baseline those who developed complications presented a larger size of the subpleural pulmonary parenchymal lesions ($P = .001$) often associated with a complex pleural effusion (63.6%, $P = .013$). Those with an uncomplicated CAP presented an air, arboriform, superficial and dynamic bronchogram, as opposed to complicated CAP which had an air and liquid bronchogram, deep, fixed ($P = .001$). At the 48-hour control in the noncomplicated CAP group, bronchogram was more frequently superficial and dynamic ($P = .050$). Pleural effusion disappeared in half cases ($P = .050$). In all patients, neutrophilic leucocytosis with increased C-reactive protein was detected and decreased at control ($P = .001$). The linear regression analyses showed the switch from a deep to a superficial bronchogram as the only explanatory variable ($r = 0.97$, $R^2 = 0.94$, $P = .001$, $t = 10.73$).

Conclusions: Our study describe early LUS features of CAP that might be able to predict the development of complicated CAP.

KEYWORDS

imaging, infections: pneumonia, TB, viral

Abbreviations: CAP, community acquired pneumonia; CBC, complete blood count; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CT, computed tomography; CXR, chest X-ray; ED, emergency department; IQR, interquartile range; LUS, lung ultrasound; PIC, pediatric intensive care unit; SD, standard deviation; SOC, standard of care; WBC, white blood cell.

1 | INTRODUCTION

Community acquired pneumonia (CAP) is a common cause of pediatric morbidity and mortality worldwide.[1] CAP diagnosis relies mainly on careful medical history and clinical examination, which has poor sensitivity and specificity[2-7]; for this reason, physicians still routinely request chest X-ray (CXR) to confirm CAP, although this is not recommended by international guidelines.[8,9]

In recent years, lung ultrasound (LUS) use has been widely studied as an alternative diagnostic tool for CAP proving to give good results.[7] LUS has a number of advantages over CXR: documents consolidation and its resolution,[10] guarantees fast execution, no radiation exposure, reproducibility and the possibility to be performed at the bedside. Published research mainly compare LUS with CXR for the diagnosis of pneumonia, without providing detailed ultrasound description of the consolidations. Moreover, those studies including a LUS follow-up during CAP treatment did not include an early (48 hours) LUS control and did not describe detailed LUS changes during treatment. This topic is of paramount importance in modern medicine, where the personalized care is becoming a new priority.[11] Noteworthy, a recent study[9] showed that LUS is still poorly studied in pediatric medicine.

Therefore, we performed this prospective study aimed at evaluating LUS features of pediatric CAP at baseline (T0) and 48 hours after beginning of antibiotic treatment (T48) and evaluate their ability to predict the development of complicated CAP.

2 | METHODS

2.1 | Study design

We prospectively analyzed patients aged from 1 month to 17 years admitted to a tertiary level pediatric hospital between 1 July 2016 and 31 July 2018, and submitted to LUS performed by a pediatrician with documented expertise in this technique. To identify patients, study sonologists were notified of a suspected CAP by the emergency department (ED) physician.

Written informed consent was obtained before data collection from a parent/guardian. Our institution's Ethical Committee approved the study (protocol 1564_2018). All patients' data were analyzed anonymously.

2.2 | Patients

The evaluating physician made the clinical diagnosis of CAP in accordance with the British Thoracic Society guidelines.[11]

At the first evaluation in the ED, all children with suspected CAP underwent: medical history; clinical evaluation; anteroposterior CXR (the pediatric radiologist on duty was aware of the indication for CXR and patient's demographics, but blinded to LUS results); blood tests including complete blood count (CBC) with white blood cell (WBC), and C-reactive protein (CRP).

The physician was blinded to LUS findings.

The physician on duty made decisions about the patient's diagnosis and treatment according to his/her own practice and without knowledge of the LUS findings, but aware of CXR and blood tests results. In our institution, the local protocol for CAP antibiotic treatment follows the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America.[8]

For discharged patients, a 48 hour outpatient control was offered; for those who accepted, a control LUS was always performed, while control blood tests (48 hours after treatment) were performed (soon after LUS) only when deemed useful by the physician.

For hospitalized patients, a 48 hour LUS control was always performed, while control blood tests (48 hours after treatment) were carried out only when requested by the physician.

The study flow is showed in Figure 1.

2.3 | Inclusion criteria

Children with a clinical diagnosis of CAP (based on history, clinical examination, blood tests, and CXR) who underwent LUS at the first examination in the ED and a second LUS 48 hours after the beginning of antibiotic therapy.

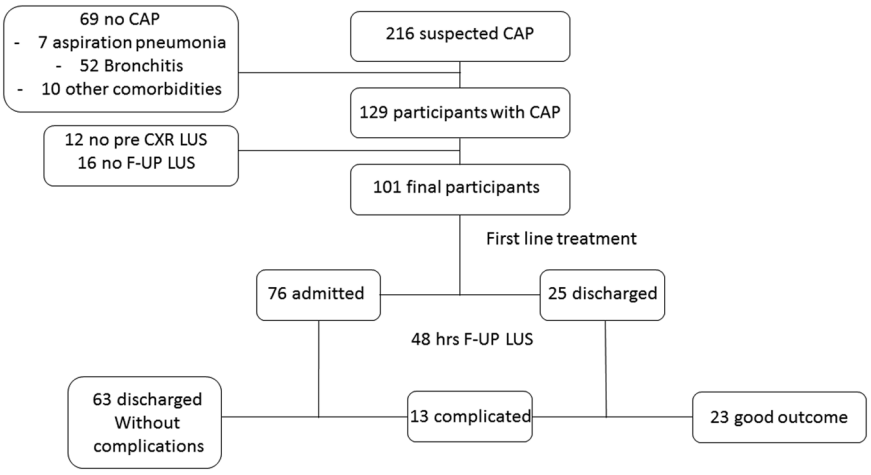

FIGURE 1 Study workflow. CAP, community acquired pneumonia; LUS, lung ultrasound

2.4 | Exclusion criteria

Patients with underlying diseases, including respiratory tract anomalies, immunodeficiency, cerebral palsy, neuromuscular diseases, congenital heart disease, and malignancy were excluded, as well as children with a prior CXR for the same illness or requiring life support or those who did not undergo LUS at 48 hours after treatment.

2.5 | CAP definitions

We defined as complicated CAP those patients requiring: admission to the Pediatric Intensive Care Unit (PICU), invasive ventilation or continuous positive airway pressure (CPAP), pleural drainage or hospitalization for a period longer than 10 days (major criteria as per reference[8]).

2.6 | Performance of LUS

LUS was performed by three pediatricians, with 5-year experience in this technique and blinded to CXR results. LUS was performed soon after CAP was suspected and before blood tests and CXR, to reduce patient discomfort. We used a portable ultrasound instrument (SonoSite M-Turbo, Esaote) with a 10 to 12-MHz linear transducer.

Ultrasonography examinations were performed following the previously described methodology.[12-15] Longitudinal and transverse sections were collected on the anterior, lateral, and posterior chest wall. Images and clips were stored and archived.

All the enrolled patients underwent a first LUS in the ED (T0) and a second (LUS) 48 hours after the beginning of antibiotic treatment (T48); the second LUS was made by the same physician that made the first one to reduce inter operator differences.

The following LUS features were recorded (Figure 2):

- size of the main lesion that we generally define as subpleural pulmonary parenchymal lesion (Consolidation and Atelectasis) (<2 cm, between 2 and 5 cm, >5 cm). We chose this cut-off since most literature refer to a 1 cm cut-off for a possible viral etiology[10];
- presence of bronchograms, its characteristics (air or fluid), morphology (arboriform or dot-like/linear), position (deep if >2 cm far from the pleura or superficial if close to the pleura), dynamicity during breath (fix, poorly dynamic, or clearly dynamic);
- presence and type of pleural effusion: simple (anechogenic and dependent to gravity) or complex (presence of septa, hyperechogenic spot, following the lung through the apex and not dependent to gravity, requiring drainage)

To ensure validity of LUS interpretation, we randomly selected 10% of our subjects and had an independent reviewer who reinterpreted LUS. We had a concordance rate of 93.3% and a kappa value of 0.71, which confirmed that the interpretation by the first rater was valid. Interobserver reliability for a positive LUS with 95% CI was defined for agreement: $\kappa = 0.81 \pm 1.00$ excellent, 0.61 ± 0.80 good, 0.41 ± 0.60 moderate, 0.21 ± 0.40 fair, greater than 0 ± 0.20 slight, and 0 absent.

2.7 | Treatment

We considered standard of care (SOC) the first line treatments (for either outpatient or inpatient) as per international guidelines[8] (amoxicilline, amoxicilline/clavulanate, ceftriaxone, cefotaxime, ampicilline, and penicilline). Those children requiring (either on diagnosis or during hospitalization) a different treatment or addition of other antibiotics or switch to ad-hoc antibiotics or treatments for more than 10 days[8] where considered as "no SOC treatments" (eg, vancomicine, carbapenems, piperacilline/tayobactam, and linezolide).

2.8 | Outcome measures

Measures of clinical outcome included the length of hospital stay, intensive care unit (ICU) hospitalization, and complicated pneumonia requiring tube thoracotomy or intubation or tracheostomy, need for a change in antibiotic therapy.

- Primary aim: to describe baseline (T0) and early changes in LUS (48 hours after treatment beginning, T48) findings;
- Secondary aims: to compare baseline (T0) and early changes in LUS (T48) findings with the development of complicated CAP.

2.8.1 | Statistical analysis

Statistical analysis was performed using the SPSS software (IBM SPSS Statistics, version 24.0, Chicago, IL). The normality of the data distribution was assessed by the Kolmogorov-Smirnov test. Values

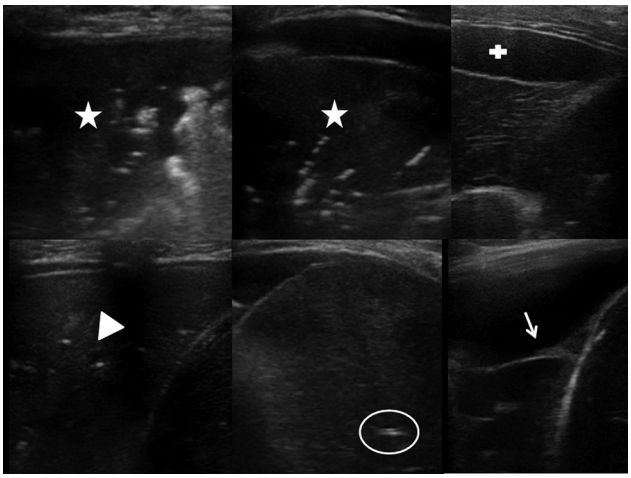

FIGURE 2 Main lung ultrasound characteristics evaluated. Arboriform, air bronchogram (white star). Puntiform/linear Bronchogram (white triangle). Deep (far from the pleura) liquid bronchogram (anaecogenic binary bronchogram not getting colored with doppler) (white circle). Simple (white cross) and complex (white arrow) pleural effusion with septae

were expressed as arithmetic means ± standard deviation (SD) for continuous variables, median, and interquartile range (IQR) for nonparametric data, or number and percentage (%) for categorical variable. The Mann-Whitney test, Student *t* test, and one-way analysis of variance (ANOVA) were used to compare nonparametric and normal data, respectively, while the χ^2 was used to compare categorical variables. The Pearson (normal data) or Spearman (nonparametric data) tests were used for correlation analysis between variables. The McNemar test was used for dichotomous data before and after 48 hours of treatment. A multiple linear regression analysis (stepwise method) using the length of hospitalization as a dependent variable and the oxygen saturation at first evaluation, the consolidation size, the therapy performed (SOC or not), the CBC and the CRP levels at the input and their variation at 48 hour control and the different aeration of the bronchogram at 48 hour LUS control (overall more aerated consolidation and more superficial bronchogram) as independent variables. $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patients' characteristics

Initially, 216 children with suspected CAP at the first ED examination underwent LUS, CXR and blood tests. ED physician made a final diagnosis of CAP on 147 of them. Out of them, eighteen patients were excluded because of congenital respiratory tract anomalies (two), heart disease (five), immunodeficiency (one), cerebral palsy (five), neuromuscular diseases (three) and malignancy (two). Twelve patients were excluded because LUS was not done before CXR, and sixteen because LUS was not done 48 hours after the beginning of treatment. A total of 101 children were enrolled in the study (Figure 1).

Table 1 summarizes demographic, clinical and laboratory findings of children with CAP. Patients with complicated and noncomplicated CAP presented similar epidemiological and clinical data.

3.2 | LUS findings

Table 2 shows main baseline (T0) LUS features of children with noncomplicated and complicated CAP. Between the two groups (complicated and noncomplicated CAP), there was no difference in the location of the subpleural pulmonary parenchymal lesions even if, in those presenting complications, bilateral consolidations were more often found ($P = .064$).

3.2.1 | Baseline LUS findings (T0)

Those who developed complicated CAP had a larger size of the subpleural pulmonary parenchymal lesions (>5 cm in 63.6% of cases, $P = .001$) often associated with pleural effusion (63.6%, $P = .013$), complex in most cases (80%, $P = .001$).

Those who developed noncomplicated CAP more often presented with air, arboriform, superficial and dynamic bronchogram, as opposed to the complicated CAP which had an air and liquid, deep, fixed or not very dynamic bronchogram ($P = .001$) (Table 3).

TABLE 1 General and clinical characteristics of the study population

	CAP	Complicated CAP	*P* value
Age, mo (IQR)	44 (20-70)	57 (16-162.5)	Ns
Males, n (%)	39 (44.3)	7 (53.8)	Ns
Chest pain, n (%)	11 (12.5)	5 (38.5)	0.28
Cough, n (%)	66 (75)	12 (92.3)	Ns
Fever, number days before ED visit (IQR)	3 (2-5)	4 (2-5)	Ns
Maximum temperature, °C (IQR)	38.2 (38.0-38.7)	38.0 (38.0-39.0)	Ns
Respiratory distress:	7 (8)	7 (53.8)	.001
Nasal fins breathing, n (%)	4 (4.5)	6 (46.2)	.001
Retractions of the jugule, n (%)	4 (4.5)	6 (46.2)	.001
Intercostal retractions, n (%)	7 (8)	9 (69.2)	.001
Diaphragmatic retractions, n (%)	6 (6.8)	8 (61.5)	.001
Wheezing, n (%)	5 (5.8)	1 (7.7)	Ns
Bronchial rhonchi, n (%)	6 (6.8)	0 (0)	Ns
Crackles, n (%)	48 (54.5)	8 (61.5)	Ns
Decreased breath sounds, n (%)	27 (30.7)	9 (69.2)	.006
Oxygen saturation in ED, % (SD)	97.3 ± 3.03	96.5 ± 0.70	Ns
Heart rate, bpm (SD)	120.67 ± 25.91	142.5 ± 3.53	.017
Breath frequency, breath/min (SD)	32.67 ± 9.78	46.5 ± 19.09	Ns

Note: Variables are expressed as frequencies (percentages), arithmetic means (± SD) or median (interquartile range, IQR).
Abbreviations: CAP, community acquired pneumonia; ED, emergency department; IQR, interquartile range; Ns, not significant.

TABLE 2 Ultrasound characteristics in patients with normal CAP and complicated CAP at T0

Ultrasound findings at T0	CAP (n = 88), %	Complicated CAP (n = 13), %	*P* values
Right lung involvement	49.4	41.7	
Left lung involvement	42.4	25.0	.064
Both lungs involvement	8.2	33.3	
Subpleural pulmonary parenchymal lesion (Consolidation and Atelectasis)			
Size (deepness)			
<2 cm	44.2	0	.001
2-5 cm	50.6	36.4	
>5 cm	5.2	63.6	
Bronchogram characteristics			
Air bronchogram	94.3	23.1	
Liquid	1.1	0	.001
Both	4.5	76.9	
Arboriform	94.3	30.8	
Puntiform	5.7	69.2	.001
Deep	17	76.9	
Sup	83	23.1	.001
Fix	1.1	46.2	
Dynamic	92.1	15.4	.001
Poorly dynamic	6.8	38.5	
Pleural characteristics			
Pleural effusion	24.7	63.6	.013
Simple plural effusion	100	20	
Complicated pleural effusion	0	80	.001

Note: Variables are expressed as percentage.
Abbreviation: CAP, community acquired pneumonia.

3.2.2 | LUS findings 48 hours after beginning of treatment (T48)

Noncomplicated CAP children had more often a superficial and dynamic bronchogram ($P = .050$). Pleural effusion disappeared in half cases (24.7% vs 13.6%, respectively, at T0 and T48, $P = .050$) (Table 4).

Complicated CAP children more often had a superficial bronchogram ($P = .034$) while no significant difference was evident in the other parameters of the bronchogram. Pleural effusions were observed in a higher number of children compared to the T0 LUS (T0 63.6% vs T48 69.2%) (Table 4).

The linear regression analyses found that the change from a deep to a superficial air bronchogram was the most significant predictor of treatment response ($r = 0.97$, $R^2 = 0.94$, $P = .001$, $t = 10.73$).

TABLE 3 Ultrasound characteristics in patients with normal CAP at T0 and T48 hours

	CAP (n = 88)		
Ultrasound findings	T0%	T48%	*P* values
Bronchogram characteristics			
Air bronchogram	94.3	96.7	
Liquid	1.1	0	Ns
Both	4.5	3.3	
Arboriform	94.3	98.4	
Puntiform	5.7	1.6	Ns
Deep	17	8.2	
Sup	83	91.8	.050
Fix	1.1	4.9	
Dynamic	92.1	93.4	
Poorly dynamic	6.8	1.6	.050
Pleural characteristics			
Pleural effusion	24.7	13.6	.050
Simple plural effusion	100	100	
Complicated pleural effusion	0		Ns

Note: Variables are expressed as percentage.
Abbreviations: CAP, community acquired pneumonia; *Ns*, not significant.

3.3 | Laboratory data

Neutrophilic leucocytosis with an increase in CRP values were detected at T0 and diminished at T48 ($P = .001$ in all cases) in both groups.

TABLE 4 Ultrasound characteristics in patients with complicated CAP at T0 and T48

	Complicated CAP (n = 13)		
Ultrasound findings	T0%	T48%	*P* values
Bronchogram characteristics			
Air bronchogram	23.1	53.8	
Liquid	0	7.7	.034
Both	76.9	38.5	
Arboriform	30.8	53.8	.083
Puntiform	69.2	46.2	
Deep	76.9	61.5	
Sup	23.1	38.5	Ns
Fix	46.2	46.2	
Dynamic	15.4	23.1	Ns
Poorly dynamic	38.5	30.8	
Pleural characteristics			
Pleural effusion	63.6	69.2	Ns
Simple plural effusion	20	33.3	
Complicated pleural effusion	80	66.7	Ns

Note: Variables are expressed as percentage.
Abbreviations: CAP, community acquired pneumonia; *Ns*, not significant.

3.4 | Treatment and outcome

Twenty-five (25.5%) were discharged directly by the ED, 76 (75.5%) were hospitalized. Length of hospitalization was 3 days (0-4) for noncomplicated CAP vs 20 days[10] for complicated CAP ($P = .001$). In 73 patients (72.3%) SOC antibiotic therapy (single in 57.5%, double in 42.5%) was started, but was changed in 5 (6.8%).

4 | DISCUSSION

Our study describes LUS features of CAP at baseline (T0) and their modifications 48 hours after the beginning of antibiotics (T48) and highlights how specific findings correlate with the development of complicated CAP. To the best of our knowledge, there are no similar studies in current literature.

To date, studies have mainly focused on LUS accuracy in comparison with CXR with good results (sensitivity of 40%-100% and specificity of 44%-100%).[8,10,12,16-32] On the contrary, our study focused on novel aspects. LUS allows the detailed description of lung pathology. As far as we know, such findings have not yet been analyzed in such a detailed way.

Interestingly, all our patients had subpleural pulmonary parenchymal lesions greater than 1 cm. A bigger lesion was strongly associated with a longer hospitalization ($P < .0001$). Lissaman et al[32] showed that 44% of patients with subcentimeter lesions improved without antibiotics and suggested they may be due to a viral infection other than a bacterial CAP. It is possible that these subcentimeter lesions represent atelectasis. Other studies also reported an improved specificity and a closer correlation with positive clinical CAP diagnoses with a LUS cut-off greater than 1 cm.[27,28,31,33-35] In our series, despite early LUS control (T48), subpleural pulmonary parenchymal lesion disappeared in 27 cases (26.7%) already after 48 hours of treatment (t48), interestingly only in those of the 1 to 2 cm lesion subgroup, supporting previous studies.

An air arboriform bronchogram was the most common finding and the majority of them presented a superficial bronchogram. Most children with a longer or complicated hospitalization had at T0 LUS a deep, fix, both air and liquid bronchograms, with a statistically significant difference compared with those with noncomplicated CAP.

The role of LUS in determining the presence and features of pleural effusions is well known, as well the prediction of complicated outcomes when complex effusions are present[10,16-19]; our study confirmed these finding (80%, $P = .001$).

Although radiological follow-up is not routinely indicated in pediatric CAP,[8] LUS represents a safe method to monitor disease progression, avoiding additional radiation exposures. To the best of our knowledge, our study is the first one evaluating ultrasound changes on an early phase of CAP treatment (48 hours). We choose the 48 hour follow-up timing aiming to features that could help physician in routine practice and clinical decisions.[8,36,37] Reissig et al,[38] despite having carried out one of the most detailed studies on this topic, performed LUS control between 5 and 8 days from the beginning of treatment and used a convex probe. Caiulo et al[18] also reported an improvement (between the 3rd and 6th day) expressed in decrease in size or disappearance of subpleural consolidations in LUS (76 of 83) with clinical improvement and drop in inflammatory laboratory markers. Ianniello et al[39] highlighted that LUS after 5 days showed a complete disappearance or decrease in size of subpleural pulmonary parenchymal lesions in 84.6% of their patients. Omran et al[40] reported the complete regression or diminished size in 81.6% of patients on day 5 of treatment. We showed that children with noncomplicated CAP had an overall improvement already at T48 LUS control, while this trend was not described in children with complicated CAP. In particular, more than 90% of children with noncomplicated CAP presented at T48 an arboriform, superficial and dynamic bronchogram ($P = .05$), while these modifications were described in less than 50% of cases in complicated CAP. This is a relevant finding if we consider that all patients, including those with complicated CAP, had a clinical improvement (no fever) and reduction in CRP and WBC, suggesting that LUS may be the best early predictor of development of complicated CAP.

Taken all together, these findings have the potential to impact daily clinical practice. The need for admission should not depend on LUS findings but on current guidelines, which are very clear and evidence based on this point.[8] On the contrary, how the clinician should follow the child with CAP for the expected response to therapy is still based on moderate-quality evidence.[8] Current guidelines state that "children on adequate therapy should demonstrate clinical and laboratory signs of improvement within 48 to 72 hours", although we showed that most children with complicated CAP had initial clinical (no more fever) and laboratory (reduction of CRP and leukocytosis) improvement. Here, LUS can provide new data to monitor treatment response and, if other studies will confirm our findings, allow developing new protocols for the follow-up of children with CAP.

Our study has some limitations: risk of selection bias was high because participants were recruited on the clinical need for imaging. Age range does not represent a homogeneous population. The sample size was relatively small allowing us to analyze a subgroup of only 13 complicated CAP. Selection bias may have occurred and some patients may have had viral pneumonia, despite our decision to enroll in the study only those patients with a diagnosis of CAP made on the basis of as many elements as possible (not relying only on imaging, but including history, signs and symptoms, and blood tests). Computed tomography imaging was not included for ethical reasons. We generally define the main lung lesions as subpleural pulmonary parenchymal lesion (including both pneumonia and atelectasia) without a strict definition between the two since this distinction is potentially confounding. Our conclusions exclusively refer to CAP in previously healthy pediatric patients. Finally, ultrasound is an operator dependent procedure.

In conclusion, our study describe early LUS features of CAP that might be able to predict the development of complicated CAP. These findings may help the physicians to better managing a child with CAP. However, further studies on pediatric CAP are necessary to confirm our findings.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

DB and AMM conceptualized and designed the study, had full access to all the data in the study and are totally accountable for the appropriateness of data and the accuracy of the data analysis. NP and PT conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript from a conceptual point of view. MCS, MB, BS, AM, SS, and CB designed the data collection instruments, collected data, carried out the initial analyses and revised the manuscript. All the authors approved the final manuscript in the present version and agreed to be accountable for everything concerning it.

DATA ACCESSIBILITY

Data sharing available upon request.

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