Turk Thorac J 2019; 20(3): 175-81 DOI: 10.5152/TurkThoracJ.2018.18087

Original Article

Diagnostic Value of Ultrasound in Detecting Causes of Pediatric Chest X-Ray Opacity

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Cite this article as: Lameh A, Seyedi SJ, Farrokh D, et al. Diagnostic value of ultrasound in detecting causes of pediatric chest X-ray opacity. Turk Thorac J 2019; 20(3): 175-81.

Abstract

OBJECTIVES: Computed tomography is considered as the diagnostic gold standard for following up the majority of pediatric chest X-ray (CXR) opacities. However, radiation, cost, and waiting times have led to search for diagnostic alternatives. This study was conducted to determine the diagnostic accuracy of the ultrasound (US) in detecting the causes of pediatric CXR opacities.

MATERIALS AND METHODS: This study was conducted on the pediatric patients with CXR opacity referring to Dr. Sheikh Hospital in Mashhad, Iran during 2016-2017. After undergoing the US exam, the patients were followed to obtain the final diagnosis based on reference standard (RF). The accuracy of the US was calculated in detection of thoracic lesions. P value <0.05 was considered to be significant.

RESULTS: The most common diagnostic cause of CXR opacity based on RF was pneumonia (n=46, 35-38%), thymus (n=37, 28-46%), bone and soft tissue mass (n=12, 9.23%), cystic lesions (n=11, 8.46%), and diaphragmatic lesions (n=10, 7.69%), as well as intrathoracic masses and empyema (n=7, 5.38%). In only four patients (3.07%), the final diagnosis based on RF was inconsistent with the US diagnosis. The diagnostic accuracy of the US was 100% in the diagnosis of bone and soft tissue masses, diaphragmatic lesions, empyema, and normal thymus, and the accuracy was 96.92% for pneumonia, and 99.23% for cystic lesions and intrathoracic masses.

CONCLUSION: Regarding the assessed diagnostic accuracy, the US can be a reliable diagnostic tool to differentiate the main cause of pediatric CXR opacity.

KEYWORDS: Chest ultrasound, diagnostic approach, pediatric lung disease

Received: *18.06.2018* ***Accepted:*** *18.10.2018* ***Available Online Date:*** *09.04.2019*

INTRODUCTION

Chest X-ray (CXR) is a routine intervention in children with respiratory complaints such as coughing, shortness of breath, and chest pain [1,2]. In this group of children, opacity is one of the more common CXR findings, which requires correct detection and decision-making by the medical practitioner [3,4]. In many cases, the pediatric CXR opacity is associated with pneumonia, and inappropriate diagnosis and misleading medications can result in high mortality [2,4,5]. Additionally, in the absence of bacterial pneumonia, not only antibiotic administration can cause antibiotic resistance in the future, but also the chance of further diagnostic measures can disappear for the patient [6,7]. Interestingly, for those pediatric chest diseases that are well diagnosed with CXR, the interpretation of the position and nature of the area is sometimes problematic by increasing opacity [3]. Further, abnormal pediatric CXR opacities cannot be easily interpreted by various configurations of the normal thymus and mediastinal masses of children [3,5]. Also, the low sensitivity and positive predictive value (PPV) of the CXR in the detection of chest disorders have led to continuous efforts to find better diagnostic modalities [8,9]. Today, the thoracic computed tomography (CT) is considered to be the recommended diagnostic gold standard in children with suspected pneumonia, and to follow-up pediatric CXR opacities and masses [3,5]. Despite the high diagnostic accuracy of CT in detecting the cause of the chest opacity, some factors like high cost, high waiting times for imaging, and exposure to high-level radiation have made use of this imaging technique not welcome as the first line of radiological evaluations [10-13].

The ultrasound (US) has high performance in the diagnosis of abdominal disorder in children as a diagnostic tool in chest disorders, except for cases of pleural effusion. Despite this, it is often introduced as unusable or unimportant tool [13,14].

In the early years of introducing the US, ventilated lung and thoracic cavity were raised as a justification for the US inefficiency in the diagnosis of pulmonary and mediastinal disorders [8]. However, technological advances in transducers and

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color flow imaging along with the acquisition of new experiences, approaches, and technologies in assessing thoracic ultrasonography over the past decade have revolutionized the US as one of the most useful tools in displaying the details of the pulmonary morphology, pleura, and mediastinal structures [3]. Moreover, the US application limited to pediatric pneumonia is on the rise in recent years [15,16]. Although different studies have introduced the US as an effective tool for the diagnosis of adult pulmonary and mediastinal problems, there are no further studies on children in order to reveal the US diagnostic accuracy in detecting chest lesions. Since the US is a rapid, easy-to-use in bedside, radiation-free, repeatable, and inexpensive method, determining the high diagnostic accuracy of the US in detecting pediatric chest lesions can help us to introduce the US as an appropriate alternative to CT.

Additionally, comparing US and CT makes it possible to determine the diagnostic accuracy of the US in determining the chest disorders. The aim of this study was to evaluate the diagnostic accuracy of ultrasonography in detecting the cause of pediatric CXR opacity.

MATERIALS AND METHODS

This prospective study was conducted on pediatric patients with unusual mediastinal or peripheral CXR opacities referring to Dr. Sheikh Pediatric Hospital in Mashhad, Iran during September 2016 to September 2017. Since entire chest US is time consuming and non-precise, all conducted USs were targeted according to the position and characteristics of the CXR opacity.

The children less than 14 years old with unusual mediastinal or peripheral pulmonary and thoracic CXR opacity by a pediatric pulmonologist as well as suspected to masses, loculation, consolidation, or diaphragmatic lesions were included. The patients who were failed for any reason, such as the impossibility of following up, to pass the final diagnosis based on gold standard were excluded from the study. Given that the diagnostic value and accuracy of US in the diagnosis of pleural effusion have already been proven [17], the patients whose cause of CXR opacity only was the pleural effusion were also excluded from the study. Due to the US limitations in the imaging, the patients with central and minor pulmonary opacities as well as the interstitial and peribronchovascular opacities were also excluded.

According to a study by Esposito et al. [15] titled `Performance of lung ultrasonography in children with community-acquired pneumonia', the sensitivity and specificity were 98% and 94%, respectively, and the prevalence of up to 50% pneumonia in the pediatric CXR opacity, the sample size was calculated to be 130 members (with the PASS software).

Initially, the gender, age, position, and characteristics of the targeted chest US purposefully were recorded for the patients. The patients then followed up on routine diagnostic guidelines such as CT scan, biopsy, surgery, or empirical treatment until they completed the final diagnosis of opacity based on the gold standard.

The reference standard (RF) for final diagnosis of intrathoracic masses including lymphoma, neuroblastoma, pleuropulmonary blastoma (PPB), germ cell tumor, sequestration, and also bone and soft tissue masses including the subcutaneous collection, Ewing sarcoma, rhabdomyosarcoma, PNET, hemangioma was CT scan and the pathology results to the biopsy or surgical specimen. For cystic lesions including hydatid cyst and bronchial cyst, the pathology results after surgical removal of lesion, and for diaphragm paralysis, eventration and diaphragmatic hernia, CT scan, and via surgical findings were considered as RF. Diagnostic confirmation of pneumonia was also performed based on the response to empirical antibiotic treatment in follow-up. The RF for empyema (loculated pleural effusion) was the results of needle aspiration and sometimes surgical findings. The RF for the diagnosis of normal thymus as the cause of opacity of upper mediastan or hemithorax in some patients undergoing CT scan, according to a physician's prescription (possibly for other lesions), were CT scan as RF. In others without CT scan, due to the lack of other pathologic findings in follow-up, thymus was considered as the ultimate diagnosis of opacity (outcome of the patient as RF). Confirmation of diagnosis with RF was done by people who were unaware of the ultrasonic findings.

In order to perform the chest US, the patients were usually placed in supine position for mediastinal and diaphragmatic lesions, and lateral or oblique positions for chest, pleural, and peripheral pulmonary lesions. If the patient was suspected to free or loculated fluid, in order to differentiate these two, it might be necessary for the patient to be in upright (sitting) position. This test was performed using an US system (H60 Samsung, South Korea) with linear or convex digital probes of 5–12 MHz. The US and final diagnosis were performed by an experienced radiologist with a minimum of 5-years experience in pediatric sonography. The radiologist who interpreted the US was unaware of the RF because it was performed after US. Therefore, this study had a double-blind design.

This study was observationally designed; and therefore, no invasive intervention was performed for the patients. Consent form was completed for each patient after a full explanation. The secrets of the patients were kept completely confidential until the end of the study, and the patients' data were coded into the statistical software. This research project was approved by the Ethics Committee of the Mashhad University of Medical Sciences (Research Project Code: 950066).

Statistical Analysis

The continuous variables were expressed as mean ± SD, and the categorical variables as frequency and percentage. Sensitivity, specificity, PPV, and negative predictive value (NPV) of the US in the detection of intrathoracic mass, bone and soft tissue mass, cystic lesions, diaphragmatic lesion, pneumonia, and empyema were calculated based on the related RF. The analytical software used in this study was Statistical Package for the Social Sciences Version 17 (SPSS Inc.; Chicago, IL, USA), and p value <0.05 was considered significant.

RESULTS

The patients were 130 children (83 males and 47 females) with the mean age of 49.06±47.21 months (27 patients aged less than 1 year, and 103 aged more than 1 year) (Tables 1,2). The position of opacity was superior mediastinum in 24 patients (18.5%), right in 62 patients (47.7%), and left in 44 patients (33.8%) of the CXR opacity. Additionally, middle zone in 13 patients (10.0%), lower zone in 42 patients (32.3%), upper zone in 34 patients (26.2%), and entire opaque hemithorax in 17 patients (13.1%) were the positions of CXR opacity (Table 3).

The most commonly final diagnoses related to the causes of CXR opacity was pneumonia and normal thymus with the frequencies of 46 (35.38%) and 37 (28.46%), respectively. The bone and soft tissue mass in 12 patients (9.23%), the cystic lesions in 11 patients (8.46%), the diaphragmatic lesions in 10 patients (7.69%), and intrathoracic mass and empyema in seven patients (5.38%) were other detected causes of CXR opacity (Table 4).

Of the 130 patients examined, the final diagnosis based on RF was inconsistent with the US diagnosis only in four patients (3.07%); including two cases of pneumonia, one case of hy-

Table 1. The prevalence of cases according to age

Age	n (%)
0–1 years	27 (20.77)
1–14 years	103 (79.23)

Table 2. The prevalence of cases according to gender

Gender	n (%)
Male	83 (63.85)
Female	47 (36.15)

Table 3. Opacity zone distribution according to CXR

Zone of opacity	Right hemithorax n (%)	Left hemithorax n (%)
Upper zone	19 (14.6)	15 (11.5)
Middle zone	8 (6.1)	5 (3.8)
Lower zone	24 (18.5)	18(13.9)
Opaque hemithorax	11 (8.5)	6 (4.6)
Superior mediastinum	24 (18.5)	

CXR: chest X-ray

Table 4. Frequency of the causes of pediatric chest X-ray opacity based on diagnostic gold standard

Causes of chest X-ray opacity		n (%)
Pneumonia		46 (35.38)
Thymus (normal)		37 (28.46)
Loculated empyema		7 (5.38)
Intrathoracic mass	Lymphoma	3 (2.30)
	Neuroblastoma	1 (0.76)
	Pleuropulmonary blastoma	1 (0.76)
	Sequestration	1 (0.76)
	Germ cell tumor	1 (0.76)
Bone and soft tissue mass	Subcutaneous collection	1 (0.76)
	Ewing sarcoma	6 (4.61)
	Rhabdomyosarcoma	1 (0.76)
	PNET	3 (2.30)
	Hemangioma	1 (0.76)
Cystic lesions	Hydatid cyst	9 (6.92)
	Bronchial cyst	2 (1.53)
Diaphragmatic lesions	Diaphragmatic hernia	5 (3.84)
	Diaphragmatic palsy	1 (0.76)
	Eventration	4 (3.07)

PNET: primitive neuroectodermal tumors

Table 5. Parameters related to the diagnostic accuracy of the ultrasound in detecting the causes of pediatric chest X-ray opacities

Causes of chest X-ray opacity, (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Pneumonia	95.83 (85.75–99.49)	97.56 (91.47–99.70)	95.83 (85.39–98.91)	97.56 (91.15–99.36)	96.92 (92.31–99.16)
Thymus	100 (90.51–100)	100 (96.11–100)	100	100	100 (97.20–100)
Bone and soft tissue mass	100 (73.54–100)	100 (96.92–100)	100	100	100 (97.20–100)
Empyema	100 (59.04–100)	100 (97.05–100)	100	100	100 (97.20–100)
Intrathoracic mass	85.71 (42.13–99.64)	100 (97.05–100)	100	99.19 (95.25–99.87)	99.23 (95.79–99.98)
Cystic lesions	90.91 (58.72–99.77)	100 (96.95–100)	100	99.17 (94.84–99.87)	99.23 (95.79–99.98)
Diaphragmatic lesions	100 (69.15–100)	100 (96.97–100)	100	100	100 (97.20–100)

datid cyst from the subgroup of cystic lesions, and one case of neuroblastoma from subgroup of intrathoracic masses.

The diagnostic accuracy of the US was 100% in the diagnosis of bone and soft tissue masses, diaphragmatic lesions, empyema, and normal thymus, and the accuracy was 96.92% for pneumonia, and 99.23% for cystic lesions and intrathoracic masses (Table 5).

DISCUSSION

The aim of this study was to determine the diagnostic value of US in assessing the cause of pediatric CXR opacity. The results showed that the US can detect various causes of CXR opacity with sensitivity and specificity nearly 100% compared with their equivalent diagnostic gold standards. The high sensitivity and specificity of the US indicates its proper position to roll out and roll in the disease. On the other hand, the PPV and the NPV of the US to detect the cause of pediatric CXR opacity were close to 100% in all cases, hereby reflecting the high accuracy of the test in the detection of patient and healthy people based on the US reports.

This is the first study that examined the US diagnostic power in evaluating the cause of pediatric CXR opacity. Therefore, its findings are of great importance. Most studies prior to our study have often expressed their experiences with the use of the US in detecting the cause of pediatric CXR opacity, and existing reports are also limited to the use of the US in the detection of the pediatric community-acquired pneumonia [9,18-20]. Several studies consistent with our study have shown that the US can be an invaluable and accurate alternative to CXR in detecting pediatric pneumonia [9,18,19,21,22]. In line with our study, a recent study claimed that the US with sensitivity and NPV close to 100% is a valuable tool in examining pediatric pulmonary consolidations [19]. Amatya et al. [23] also reported that bedside lung US in children has a higher sensitivity to CXR in detecting pneumonia. In the meta-analysis performed on eight studies, it was shown that the sensitivity and specificity of the US in detecting pneumonia were 96% and 93%, respectively, very close to our findings, while these values were 96% and 84% for the CXR [16]. Another meta-analysis (2018) reported that the US of pediatric pulmonary is associated with the sensitivity and specificity of about 95% [24]. The difference in the diagnostic standard criteria of pneumonia, the age, body size, and chest of the children and the absence of certain standard techniques for the evaluation of the lung by the US seem to be possible reasons for a slight difference in the findings of the studies [9,16,21,23]. However, it should be noted that the use of US in detecting pneumonia is accompanied by restrictions as well, such that the infection should be in the pleural level for the US detection of pneumonia, because the examination of central structures by the US is less possible due to the presence of barrier made by the pleural-lung interface [9]. Additionally, the consolidation should be in the intercostal window, meaning a small number of pneumonia cases (about 8% in adults) are undetectable by the US [25]. Further, it should not be forgotten that the US, especially in children, is highly dependent on the operator, and reportedly has a strong ability to identify the characteristics of hilar and mediastinal opacities, the apex of lung, left lower lobe, and subcapsular regions [26]. However, various studies have shown that a short-term training course, even for a few days, can also dramatically improve the ability of the US to detect pulmonary pneumonia compared to the CXR [18]. On the other hand, studies have shown that the ability of the US operators trained in the lung US for only 30 minutes was no different in detecting pneumonia with those who had more than two years of experience [27]. Therefore, it seems that the position of the US in detecting pediatric pneumonia can be considered beyond the CXR or an alternative (Figure 1).

What makes our study different from other studies is to present the parameters of the diagnostic value of the US in detecting other causes of pediatric CXR opacities, other than pneumonia. In our study, the diagnostic value of the US for bone and soft tissue mass, empyema intrathoracic mass, and cystic lesions and diaphragmatic lesions was also reported for the first time in the form of a pediatric study.

As expected, in our study, the thymus was one of the most prevalent causes of pediatric CXR opacity. The thymus is the most commonly occurring extracardiac mediastinal structure in the pediatric chest, which clearly appears in the pediatric CXR, although variations in size and position occasionally cause ambiguity and need more imaging [28,29], which also occurred in our study. The thymus was reportedly the cause of opacity in about 30% of children (Figure 2). This finding is important because it shows that if children are under the US since onset, the need for more imaging action and subsequently the cost of treatment might be reduced up to 30%.

The intrathoracic masses, cystic lesions, diaphragmatic lesions, and bone and soft tissue masses were among the less common but diagnosed items in the US, with a frequency ranging from 7.5% to 9%.The malignant disorders occupying the pleural space are much less common in children than in adults, but they can occur with Wilms' tumor, neuroblastoma, leukemia, and sarcoma [29,30]. The primary pulmonary neoplasms are, of course, very rare in children. The pulmonary blastoma is one of the most commonly occurring pediatric pulmonary masses. It usually begins as a peripheral lesion, which often occurs with increasing size before clinical presentation [21]. In our study, we observed one sequestration, which is considered as one of the congenital lung parenchymal masses, which is seen in the US view as an echogenic homozygous structure with minor cystic lesions [31]. Intralobar sequestration is often found in the left lower lobes and extralobar sequestration in the lower left side of the chest, which is associated with recurrent infections or persistent radiographic opacity (29). In our study, the extralobar sequestration was observed at the top of the right diaphragm as a mass opacity, which had an echotexture specific to the sequestration in the US view (Figure 1). In our study, lymphoma was the cause of intrathoracic mass more than other diagnoses were. Anterior mediastinum is one of the most common conditions for a type of neoplasm, especially lymphoma [29]. The majority of children with lymphoma, especially Hodgkin's lymphoma, have anterior mediastinal involvement [32]. Consideration of clinical symptoms of children, especially fever, weight loss, and respiratory complaints, along with findings from the US suggesting lymphoma, such as discrete masses, nodular enlargement, or disseminated

thymic infiltration, can lead physicians to a better diagnosis [28,29]. In our study, three children were diagnosed with suspected lymphoma during the US, which was confirmed by the diagnostic gold standard. In these three children, the relevant clinical manifestations along with the US findings, particularly conglomerate masses and heterogeneous thymic infiltration, greatly helped in diagnosis (Figure 2). In mediastinal germ cell tumors, the calcification areas within enlarged and infiltrative thymus were a clear diagnostic item (Figure 2).

In addition to intrathoracic masses, our diagnostic accuracy of the US in detecting cystic lesions was also reported to be 99%. In 11 of the cases diagnosed with cystic lesions, in addition to the pulmonary hydatid cysts, two bronchial cystic lesions were detected using the US (Figure 2). However, the diagnosis of pulmonary cysts using US is a report that is rarely mentioned in previous studies [33,34], which may be due to the low prevalence of hydatid cysts in advanced societies and the central nature of bronchogenic cysts. Our study shows that the US can also detect these lesions due to the high prevalence of hydatid cyst in our society (developing countries). Based on our experience, the diagnosis of bronchogenic cysts with deep probe from the heart window and mediastinum, and the diagnosis of hydatid cysts with targeted chest US were performed taking into account the mass position in the CXR. The presence of cystic lesions in the center of the pulmonary consolidation, which has a bilayer wall, is specific view of hydatid cyst. In most patients, due to the perforation of hydatid cysts in the presentation, the inner wall of the cysts is wrinkled and folded (Figure 3).

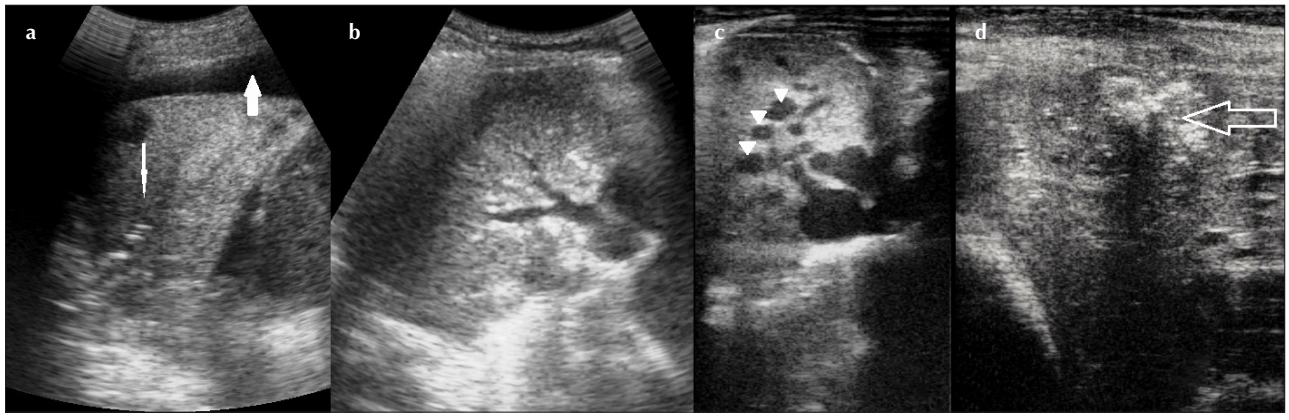

Figure 1. a-d. The ultrasound images of lung lesions. (a) Pneumonic consolidation with hypoechoic necrotic area (thin arrow) in left lower lobe associated with para-pneumonic effusion (thick arrow). (b) Collapse consolidation of right upper lobe. Sonographic air bronchogram is not seen due to mucus plaque bronchial obstruction. (c) Echogenic lung with small cysts (multiple arrowhead) due to lung sequestration. (d) Calcified metastatic mass (arrow) in background of consolidation in patient with pulmonary metastatic osteosarcoma

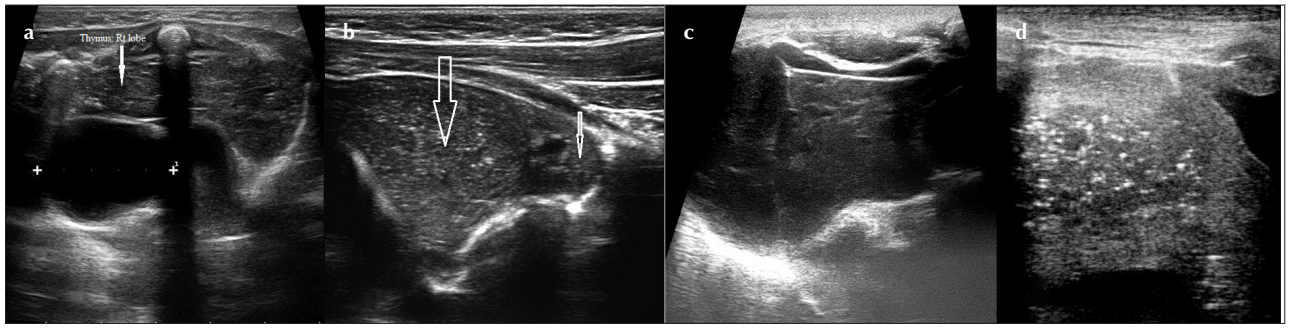

Figure 2. a-d. Normal thymus and associated lesions. (a) Bronchial cyst (between + markers) in posterior border of right lobe of thymus (arrow). (b) Small part of collapsed lobe (thin arrow) due to bronchial atresia adjacent to left lobe of normal hyperplastic thymus (thick arrow). (c,d) Thymus infiltration by lymphoma (c) and germ cell tumor (d)

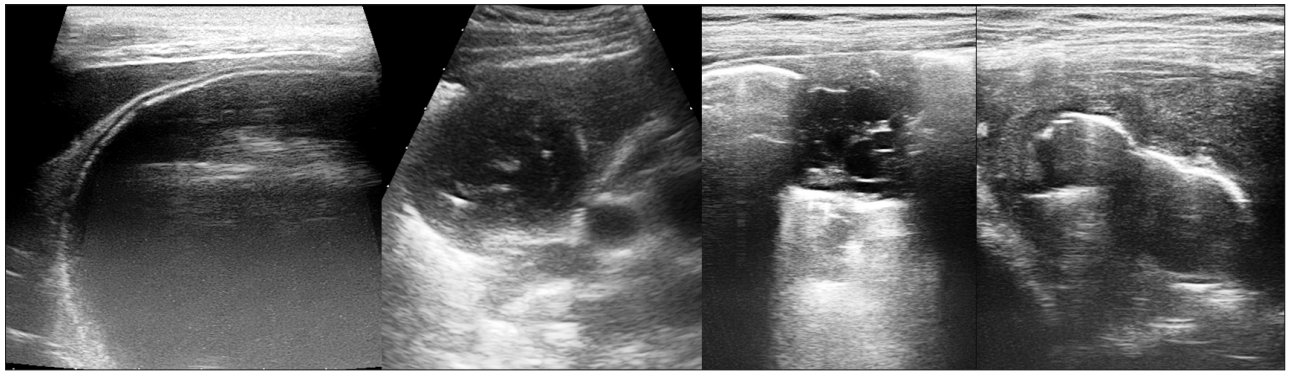

Figure 3. The ultrasonic views of some cases with simple and complicated hydatid cyst of lung

Among the bone and soft tissue masses in our study, the most common mass was related to Ewing sarcoma, in which half of the masses detected from the bone and soft tissue mass were associated with this malignancy. What contributed to the diagnosis of Ewing sarcoma in this study was the observation of the corrosion and irregularity of one or two ribs adjacent mainly to the intrathoracic mass.

The US is a valuable tool in diaphragm examination, which provides diagnosis of delineation of masses surrounding diaphragm, contour and hernia abnormalities, as well as movements [35-37]. Congenital diaphragmatic hernia is usually located on the left diaphragm, and it is poorly detected by the CXR [29]. The eventration of the diaphragm is also the condition that occurs due to the congenital weak and thin central muscles or tendons, which is detected in the US with an intact hemidiaphragm [38,39]. In our study, the diaphragmatic lesions were detected in about 8% of the patients. The diagnostic consistency of the US with the diagnostic gold standard along with a diagnostic accuracy of 100% from the US showed the high ability of this imaging tool in detecting hernia, palsy, and eventration. The liver and spleen have created the best window for diaphragm examination and its lesions. However, the use of the chest US in detecting the diaphragmatic lesions, especially congenital hernia, has already been confirmed, and our findings will only emphasize this finding [40,41].

Overall, it should be noted that although plain CXR is sufficient for chest examination in many cases, sometimes further imaging is needed. Currently, CT scan and MRI provide acceptable images, but these techniques are limited by the need to prescribe sedative, high costs, and exposure to radiation, and sometimes contrast media. According to the findings of this study, the US usage seems to provide essential clinical information with high sensitivity and specificity without the need for sedation, the risks of radiation, and contrast media. Additionally, if the US is unable to show all the required information, it can be at least a guide to determine the most relevant and definitive next imaging needed for further examination [9,20,29]. Besides, the US can be a good guide for intervention, especially in children.

This study had several limitations. The first was the small sample size as some of the causes of opacity, so that about a few lesions were found to be in about seven patients, leading to not being able of fully generalizing the findings. Although the sensitivity of US in detecting the causes of pediatric CXR opacity was high, but non-restricted 95% confidence interval in this diagnostic parameter except for pneumonia and thymus showed the small sample size and reduced power generalization of the results on the other causes of CXR opacities, highlighting the need for further studies in this area.

The other limitation of this study was the selection method of the patients. The results of this study are related to the pediatric patients with unusual mediastinal or peripheral thoracic opacities in CXR and suspected to masses, loculation, consolidation, or diaphragmatic lesions, but not the central and minor pulmonary opacities and peribronchovascular opacities with respect to the US restriction. Therefore, the generalization of the results to all chest opacity-related lesions is impossible.

Also, since the entire chest US is time consuming, all USs were conducted purposefully according to the position and characteristics of the CXR opacity.

Although our findings indicated that the purposeful diagnostic accuracy of the US is high enough to detect empyema, intrathoracic mass, and bone and soft tissue mass, as well as diaphragmatic lesions and cystic lesions, further studies are needed to determine the best technical approaches for the US, and to confirm the findings of this study.

Considering the findings of this research as well as of other studies, the US can be used as an appropriate imaging modality for the diagnosis of pediatric thoracic opacities other than interstitial and peri-bronchovascular lesions.

As previously mentioned, various studies have shown that a short, even a few-days training, can enhance the ability to detect pneumonia with the help of US. Therefore, holding special pediatric chest sonography training courses can promote the diagnosis of pneumonia and other lesions by radiologists, and serve as a substitute for more invasive imaging techniques.

According to our findings, the targeted chest US has a high potential for rapid and accurate diagnosis of the causes of different unusual thoracic opacities in pediatric patients, especially in the patients suspected to mediastinal or peripheral pulmonary masses, loculation, consolidation, or diaphragmatic lesions. Considering the findings of this research and of other studies, the US can be used as an appropriate imaging intervention for the differentiation of pediatric thoracic opacities other than interstitial and peri-bronchovascular lesions. Further studies are needed to determine the best diagnostic approaches in pediatric pulmonary opacities, especially compared with CT scan, and to confirm the findings of this study.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Mashhad University of Medical Sciences (IR.MUMS.FM.REC1395.336) (decision no: 1395.336, date: 2016/10/26).

Informed Consent: Verbal informed consent was obtained from the parents of the patients patient who participated in this study.

Peer-review: Externally peer-reviewed

Author Contributions: Concept – S.A.A., S.J.S., D.F.; Design – A.L., S.L.; Supervision – S.A.A., S.J.S., A.L.; Resources – S.A.A., A.L., D.F.; Materials – S.J.S.; Data Collection and/or Processing – S.J.S., A.L.; Analysis and/or Interpretation – S.J.S., A.L.; Writing Manuscript – S.A.A., A.L., S.L.; Critical Review –S.A.A., S.J.S.; Other – S.L., A.L., D.F.

Acknowledgment: The authors wish to thank the staff of radiology, surgery, pathology and pulmonary wards of Dr. Sheikh hospital for their kinds assistance and support to data collection.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This article has been adopted from a research project with the Grant number 950066 and a Specialty Thesis on Ra-

diology written by Dr. Ahmad Reza Lame with code of T4904, funded by the Deputy of Research. We acknowledge the financial support provided by Mashhad University of Medical Sciences (MUMS).

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