ISSN 2644-3260 (online)

# Artificial Intelligence in *Medical Imaging*

*Artif Intell Med Imaging* 2022 February 28; 3(1): 1-20

Published by Baishideng Publishing Group Inc

AIMI

Artificial Intelligence in Medical Imaging

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Bimonthly Volume 3 Number 1 February 28, 2022

## MINIREVIEWS

*Artificial Intelligence in Medical Imaging*

**Bimonthly Volume 3 Number 1 February 28, 2022**

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## ABOUT COVER

Editorial Board Member of *Artificial Intelligence in Medical Imaging*, Erdal Karavaş, MD, MSc, Associate Professor, Department of Radiology, Erzincan Binali Yildirim University, Erzincan 24100, Turkey. erdalkaravas@hotmail.com

## AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Medical Imaging* (*AIMI*, *Artif Intell Med Imaging*) is to provide scholars and readers from various fields of artificial intelligence in medical imaging with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*AIMI* mainly publishes articles reporting research results obtained in the field of artificial intelligence in medical imaging and covering a wide range of topics, including artificial intelligence in radiology, pathology image analysis, endoscopy, molecular imaging, and ultrasonography.

## INDEXING/ABSTRACTING

The *AIMI* is now abstracted and indexed in Reference Citation Analysis, China Science and Technology Journal Database.

## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*Artificial Intelligence in Medical Imaging*

**ISSN**
ISSN 2644-3260 (online)

**LAUNCH DATE**
June 28, 2020

**FREQUENCY**
Bimonthly



**PUBLICATION DATE**
February 28, 2022

Artificial Intelligence in Medical Imaging

Submit a Manuscript: https://www.f6publishing.com

*Artif Intell Med Imaging* 2022 February 28; 3(1): 1-7

DOI: 10.35711/aimi.v3.i1.1

ISSN 2644-3260 (online)

*MINIREVIEWS*

# Applications of artificial intelligence in common pulmonary diseases

Saiara Choudhury, Asad Chohan, Rahul Dadhwal, Abhay P Vakil, Rene Franco, Pahnwat Tonya Taweesedt

**Specialty type:** Respiratory system

**Provenance and peer review:** Invited article; externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): D, D, D
Grade E (Poor): 0

**P-Reviewer:** Hanada E, Morilla I, Muneer A, Wan XH, Wang P, Zhang W

**Received:** December 13, 2021
**Peer-review started:** December 13, 2021
**First decision:** January 26, 2022
**Revised:** February 14, 2022
**Accepted:** February 17, 2022
**Article in press:** February 17, 2022
**Published online:** February 28, 2022

**Saiara Choudhury, Asad Chohan, Rahul Dadhwal, Abhay P Vakil, Rene Franco, Pahnwat Tonya Taweesedt,** Department of Pulmonary Medicine, Corpus Christi Medical Center, Corpus Christi, TX 78411, United States

**Corresponding author:** Pahnwat Tonya Taweesedt, MD, Academic Fellow, Department of Pulmonary Medicine, Corpus Christi Medical Center, 3315 S Alameda St., Corpus Christi, TX 78411, United States. pahnwatt@gmail.com

## Abstract

Artificial intelligence (AI) is a branch of computer science where machines are trained to imitate human-level intelligence and perform well-defined tasks. AI can provide accurate results as well as analyze vast amounts of data that cannot be analyzed *via* conventional statistical methods. AI has been utilized in pulmonary medicine for almost two decades and its utilization continues to expand. AI can help in making diagnoses and predicting outcomes in pulmonary diseases based on clinical data, chest imaging, lung pathology, and pulmonary function testing. AI-based applications enable physicians to use enormous amounts of data and improve their precision in the treatment of pulmonary diseases. Given the growing role of AI in pulmonary medicine, it is important for practitioners caring for patients with pulmonary diseases to understand how AI can work in order to implement it into clinical practices and improve patient care. The goal of this mini-review is to discuss the use of AI in pulmonary medicine and imaging in cases of obstructive lung disease, interstitial lung disease, infections, nodules, and lung cancer.

**Key Words:** Artificial intelligence; Machine learning; Imaging; Lung; Respiratory; Pulmonary disease; Coronavirus disease 2019



**Core Tip:** Artificial Intelligence (AI) has the potential to have a tremendous influence when dealing with pulmonary diseases. This review provides a glimpse of AI application in pulmonary medicine and explains how AI uses imaging data to facilitate precision medicine in our data-driven era.

**Citation:** Choudhury S, Chohan A, Dadhwal R, Vakil AP, Franco R, Taweesedt PT. Applications of artificial intelligence in common pulmonary diseases. *Artif Intell Med Imaging* 2022; 3(1): 1-7
**URL:** https://www.wjgnet.com/2644-3260/full/v3/i1/1.htm
**DOI:** https://dx.doi.org/10.35711/aimi.v3.i1.1

## INTRODUCTION

Artificial Intelligence (AI) is a branch of computer science that aims to imitate human thinking ability, learning, planning, and reasoning to solve complex problems. In 1956, scientists began theorizing a computer's ability to learn new information by analyzing data which led to the beginning of the field of AI[1]. While the terms AI, machine learning and deep learning are often used similarly, the relationship between them needs to be clarified to avoid confusion. AI is the overall concept of the simulation of human intelligence using computer systems[2]. Meanwhile, machine learning (ML) is a field of AI which provides knowledge or information using its capability of learning and analyzing massive amounts of data from larger datasets including more variables than conventional statistical methods. Machine learning uses various algorithms to process data, such as supervised learning, unsupervised learning and reinforced learning[1]. Supervised learning involves the computer recognizing patterns from data using guidance. Whereas, unsupervised learning involves pattern recognition by the computer without any guidance[2]. Reinforced learning has the ability to recognize and analyze data without any labels, by using incremental positive or negative feedback[3]. Deep learning is a subset of ML that enables the algorithm to learn from a training data set and apply that to fulfill intended tasks to a new data set[2]. As healthcare data has become increasingly complex, AI has the potential to have a significant influence on medical data analysis and medical practice.

AI has been implemented in many fields of medicine to facilitate precision medicine by predicting outcomes, diagnosis, and therapeutic results. AI may assist in diagnosis of different diseases by recognizing the images from different parts of the body, predicting mortality in the critical care unit, classifying skin biopsies, and identifying new genotypes in heart failure. The US Food and Drug Administration (FDA) and Conformité Européenne (CE)-marked have approved more than 300 AI-based software/medical devices[4,6]. Many of them are related to pulmonary imaging (Table 1)[4,6].

In the 1980s, AI was initially introduced into pulmonary medicine to interpret lung function tests[5]. Since then, AI has been applied in various pulmonary diseases, including, but not limited to obstructive lung diseases, pulmonary infections, interstitial lung disease, and malignancy[6]. Given its widespread use in pulmonary medicine, it is important for pulmonologists to have a general understanding of the utilization of AI in this field and how it can aid them in caring for patients. In this narrative mini-review, we provided an overview of the pulmonary diseases that are commonly diagnosed and managed by general pulmonologists for which AI has been applied including obstructive lung disease, interstitial lung disease, pulmonary tuberculosis (TB), coronavirus disease 2019 (COVID-19) pneumonia, lung nodules and lung cancer (Figure 1.).

## METHOD

PubMed was searched from inception to November 30, 2021, using keywords: "artificial intelligence, lung disease", " artificial intelligence, pulmonary disease", "artificial intelligence, COPD, asthma", " artificial intelligence, interstitial lung disease", "artificial intelligence, tuberculosis", "artificial intelligence, COVID-19", and "artificial intelligence, lung nodule, lung cancer". All types of published publications were included, *e.g.*, reviews, observational studies, and meta-analyses. We prioritized recent articles within five years in this narrative mini-review.

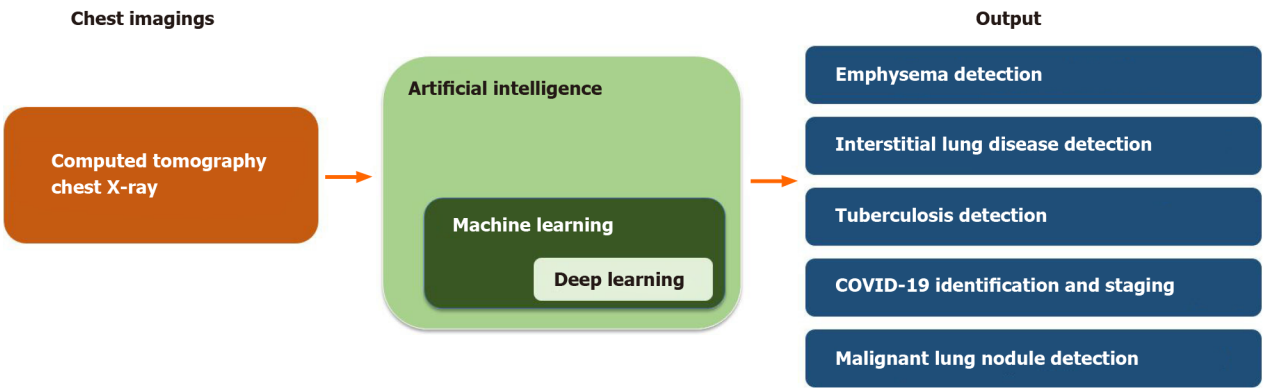
## OBSTRUCTIVE LUNG DISEASES

The gold standard of diagnosis in obstructive lung diseases like asthma and chronic obstructive pulmonary disease (COPD) involves a combination of signs, symptoms, and spirometry. While AI cannot replace the clinicians' role, it can complement clinicians' interpretation of the data available at the bedside. A study by Topalovic *et al*[7] compared the accuracy of pulmonologists' interpretation of pulmonary function testing to an AI-based software that used more than 1430 historical patient cases. Both groups were asked to study 50 patient cases and correctly interpret the pulmonary function test while placing them in diagnostic categories. AI-based software was found to outperform the pulmonologist interpretation by a substantial margin[7].

**Table 1 Example of Conformité Européenne (CE)-marked, US Food and Drug Administration (FDA)-approved or FDA-permitted artificial intelligence devices**

| Pulmonary conditions | AI device/algorithm | Imaging | Brief description |
|---|---|---|---|
| Chronic obstructive pulmonary disease | Lung density analysis software | Chest CT | Uses three-dimensional segmentation of the lungs, volumetric analysis and density evaluations from CT images to aid in diagnosis and progression of the disease |
| | LungQ software | Chest CT | Quantitative analysis of lung volume. Airway morphology analysis |
| Interstitial lung disease | LungPrint Discovery | Chest CT | Lung tissue and airway evaluation. Quantitative analysis using deep learning to detect interstitial lung disease and chronic obstructive lung disease |
| | Lung Texture Analysis | Chest CT | Transforms a standard chest CT into a detailed map. Lung textures quantification |
| Pulmonary infection | Icolung | Non-contrast Chest CT | Detects COVID-19 at an early stage and quantify the extent of lung lesions |
| | InferRead CT pneumonia | Chest CT | Real-time identification. Alerts of suspected pneumonia cases |
| Lung nodule | Syngo.CT Lung CAD | Multidetector Chest CT | Computer-aid detection tool designed to detect solid pulmonary nodules using convolutional neural network. To be used as the second reader. |
| | AI-Rad Companion (Pulmonary) | CT DICOM chest | Quantitative and qualitative analysis using deep learning. Segmentation of lung lobes and identification of lesions |
| | Temporal Comparison software | Chest X-ray | The new image is superimposed on the old image to detect changes in the lung parenchyma. |
| | ClearRead CT | CT chest | Lung nodule detection asymptomatic population |

COVID-19: Coronavirus disease-2019; CT: Computed tomography; DICOM: Digital imaging and communication.




**DOI**: 10.35711/aimi.v3.i1.1 

**Figure 1 Representative diagram showing examples of artificial intelligence applications in pulmonary diseases.** COVID-19: Coronavirus disease-2019.

### *COPD*

According to the Global Strategy for Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) reports 2022, COPD is one of the top three causes of death in the world[8]. Moll *et al*[9] also proposed a machine learning mortality prediction model for patients with COPD based on six-minute walk tests, percent predicted of forced expiratory volume in 1 second (FEV1), and age. While the gold standard of diagnosis of COPD is spirometry, studies have suggested that artificial intelligence and deep learning can potentially be utilized to screen patients for COPD. Tang *et al*[10] suggests that low dose computed tomography (CT) screening of the lungs of both smokers and ex-smokers can be examined using deep residual networks to identify patients who may have COPD but remain undiagnosed. AI has also been used to characterize patients already diagnosed with COPD. The Genetic Epidemiology Study (COPDGene) is one of the largest data sets obtained over ten years, consisting of chest imaging, spirometry, and molecular data from patients with COPD. This has been used as the source for multiple studies that have related specific COPD phenotypes to genetic and molecular mechanisms and has led to the prediction of the disease progression of various COPD

subtypes[11]. A study by Fischer *et al*[12] describes an algorithm that can perform lung lobe segmentation and emphysema quantification, which has been shown to correlate with different GOLD stages in patients with COPD per their spirometry data. Furthermore, AI-based applications have also been suggested to help patients identify if they may be having an exacerbation at home and when they should seek help from a medical professional[13]. This can promote patient responsibility and potentially save on resources, including emergency department visits.

### *Asthma*

Asthma is an intermittent and reversible obstructive lung disease with multiple phenotypes. AI may improve diagnosis, phenotype classification, prediction of asthma exacerbations and treatment response [1,15]. Multiple studies have shown good accuracy of ML-based algorithms in screening and diagnosis of asthma in adult patients[1]. In regards to phenotype classification, when using the machine learning approach as well as cluster analysis, the highest corticosteroid-responsiveness phenotype was identified in patients with low pulmonary function, high serum eosinophils, nasal polyps, and late-onset asthma [14]. The least corticosteroid-responsiveness phenotype was also found in young, obese females with early-onset asthma[14]. In another study, Qin *et al*[15] adopted deep learning algorithms-based high-resolution computed tomography (HRCT) chest images to assess small airway thickness with the aim of steroids response evaluation in asthma patients with small airway obstruction. Phenotype identification can help tailor asthma management and possibly improve outcomes.

## INTERSTITIAL LUNG DISEASE

Interstitial lung disease (ILD) is an umbrella term that encompasses all disease processes that can cause pleural/parenchymal inflammation and scarring. Deep learning algorithms can help with the diagnosis of ILD using HRCT chest images. In a case-control study by Walsh *et al*[16], a database of 1157 de-identified HRCT images showing evidence of diffuse fibrotic lung disease were classified using the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) idiopathic pulmonary fibrosis guidelines. These images were divided into multiple groups and separately read by a deep learning algorithm and 91 thoracic radiologists. Walsh *et al*[16] found that the algorithm outperformed thoracic radiologists' interpretation of HRCT images with the median accuracy of 73.3% *vs* 70.7%, respectively. This study showed that deep learning algorithms could serve as a valuable tool in the diagnosis of ILD. Similarly, Choe *et al*[17] has revealed that deep learning increases the diagnostic accuracy of chronic hypersensitivity pneumonitis, cryptogenic organizing pneumonia, nonspecific interstitial pneumonia, and usual interstitial pneumonia patterns. Other studies have used AI algorithms to evaluate HRCT images of patients with interstitial pulmonary fibrosis and have successfully been able to quantify airway volumes and parenchymal lesions[17,18].

## PULMONARY INFECTIONS

The utilization of AI has also been investigated in multiple pulmonary infections. Here, we briefly review the utilization of AI in pulmonary tuberculosis and COVID-19.

### *Tuberculosis*

Tuberculosis (TB) remains a significant cause of mortality in many parts of the world. Due to the variable presentations of TB in chest radiography, diagnosis remains a challenge. The first conventional computer-aided diagnosis (CAD) was made in 2016 to aid in the detection of TB. Over the years, investigators have also developed multiple CAD algorithms that can detect various radiographic findings in TB, for example, cavitary and focal TB[19]. In addition to diagnosis, AI can be helpful in other aspects of TB care as well. AI has been suggested as an aid to review records, identify symptomatic patterns, surveillance, and factors that may contribute to the treatment and medication adherence failure in TB [20]. Doshi *et al*[21] describe innovative ways in which AI-based software can provide access to care and facilitate the management of TB patients worldwide.

### *COVID-19*

In recent times, COVID-19 has taken the world by storm. Morbidity and mortality around the world have risen as treatment options for COVID-19 remain largely experimental. AI software has been developed to aid in the early diagnosis and prognostication of patients with COVID-19. In a retrospective, multi-center study by Li *et al*[22], a deep learning model, called COVID-19 detection neural network was developed to identify CT findings of COVID-19 infection and differentiate it from CT findings in community-acquired pneumonia. Another study developed a deep learning convolution neural network to effectively stage the severity of COVID-19 infection *via* scoring of various

radiographic features[23]. This can help in early prognostication of the disease, which can lead to making early treatment decisions. Another study by Burdick *et al*[24] used ML algorithm to build a model which uses inputs of diastolic blood pressure, systolic blood pressure, heart rate, temperature, respiratory rate, oxygen saturation, white blood cell, platelet count, lactate, blood urea nitrogen, creatinine, and bilirubin to predict the need for mechanical ventilation. Furthermore, investigators have developed deep learning algorithms which help to identify protein structures and shapes. The data provided using this algorithm has been invaluable in the development of the COVID-19 vaccine[6].

## PULMONARY NODULES AND LUNG MALIGNANCY

Despite recent advances in the treatment of pulmonary malignancies, the World Health Organization considers them among the deadliest of all solid malignancies[25]. Early and accurate diagnosis remains paramount in improving patient outcomes. CAD systems use deep learning algorithms as an aid for radiologists to analyze CT images by lung segmentation and provide a more focused analysis that will allow nodule detection and classification. One such state-of-the-art algorithm implemented by Siemen Healthcare uses statistical finite element analysis or three-dimensional lung segmentation in adversarial neural network training[26]. A study by Chauvie *et al*[27] compared different machine learning algorithms and lung-RADs criteria and concluded that neural network algorithms enhanced the positive predictive value in chest digital tomosynthesis in lung cancer detection. One identified disadvantage of deep learning is that it does not provide uniform features for identifying malignant versus benign nodules. This problem has been addressed using a method called Radiomics[28]. Radiomics uses features from one image in order to provide data-characterization algorithms that helps to identify similar features in new data. This tool can help in finding characteristics of malignancies that can be otherwise missed by human experts. The combination of Radiomics and deep learning promises the ability to provide radiologists around the world an advantage in diagnosing pulmonary malignancies. Finally, a study by Afshar *et al*[29] has proposed a deep learning-based Radiomics model to predict the time-to-event outcome prediction, that utilizes raw images of CT and PET (Positron Emission Tomography) scans and can calculate the image-based risk of death or recurrence, for each patient.

## LIMITATIONS OF AI IN CLINICAL PRACTICE

Despite the promising outcomes of AI, small or unstructured databases and missing data may result in unsatisfactory AI quality. For example, in the diagnosis of lung nodules and lung malignancy, the software's ability is usually compared to the ability of expert radiologists. However, since the ultimate goal is to diagnose malignancies and not just identify lung nodules, algorithms should be made to focus on identifying malignancies with a different reference standard[30]. Similarly, AI poses other limitations as well. For example, characteristics of CT imaging are being primarily used as an input for AI algorithm to diagnose early COVID-19 infection. However, it should be noted that while CT scan has high sensitivity it does not have very high specificity for COVID-19. So, diagnosing the disease based solely on CT images with the help of AI may be erroneous[31]. Therefore, while AI has many advantages, it is important to keep these limitations in mind. Finally, cooperation between physicians and AI researchers is needed to be able to develop well-structured AI applications that can be validated in real-world study before launching AI models into clinical fields.

## CONCLUSION

The implementation of AI and machine learning algorithms is an evolving and relevant topic in pulmonary medicine. Human errors can occur in the medical field. It can be associated with missed, late, and incorrect diagnoses leading to health and economic burden. AI is an efficient tool that can be implemented to prevent this problem by aiding in the fast, accurate, and early diagnosis, prognostication, as well as treatment of pulmonary diseases. Nonetheless, the lack of knowledge and confidence in applying AI into practice may hinder the utilization of AI in the medical field. Moreover, well-performed AI algorithms require a large well quality database. Physician and AI algorithm developers should work closely to minimize these limitations. While AI alone cannot replace clinician expertise, it can add to the armamentarium and improve patient care and healthcare worldwide.

## FOOTNOTES

**Author contributions:** Choudhury S performed the majority of the writing; Chohan AA provided the input in writing the paper; Dadhwal R provided the input in writing the paper; Abhay V provided the input in writing the paper;

Franco R provided the input in writing the paper; Taweesedt PT designed the outline and coordinated the writing of the paper.

**Conflict-of-interest statement:** All authors declare that they have no conflict of interest to report.



**Country/Territory of origin:** United States

**ORCID number:** Saiara Choudhury 0000-0001-7225-4905; Asad Chohan 0000-0002-1801-9792; Rahul Dadhwal 0000-0001-6963-1466; Abhay P Vakil 0000-0003-4947-0233; Rene Franco 0000-0002-0684-7732; Pahnwat Tonya Taweesedt 0000-0002-5791-6920.

**S-Editor:** Liu JH
**L-Editor:** A
**P-Editor:** Liu JH

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*Artif Intell Med Imaging* 2022 February 28; 3(1): 8-20

DOI: 10.35711/aimi.v3.i1.8

ISSN 2644-3260 (online)

*MINIREVIEWS*

# Chest ultrasound in neonates: What neonatologists should know

Adel Salah Bediwy, Mohammed Al-Biltagi, Jameel Ahmed Nazeer, Nermin Kamal Saeed

**Specialty type:** Pediatrics

**Provenance and peer review:** Invited article; externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Haurylenka D, Trovato G

**Received:** January 6, 2022
**Peer-review started:** January 6, 2022
**First decision:** February 10, 2022
**Revised:** February 12, 2022
**Accepted:** February 21, 2022
**Article in press:** February 21, 2022
**Published online:** February 28, 2022

**Adel Salah Bediwy,** Department of Chest Disease, Faculty of Medicine, Tanta University, Tanta 31511, Algharbia, Egypt

**Adel Salah Bediwy,** Department of Pulmonology, University Medical Center, Arabian Gulf University, Manama 26671, Manama, Bahrain

**Mohammed Al-Biltagi,** Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31511, Algharbia, Egypt

**Mohammed Al-Biltagi,** Department of Pediatrics, University Medical Center, Arabian Gulf University, Manama 26671, Manama, Bahrain

**Jameel Ahmed Nazeer,** Department of Radiology, University Medical center, King Abdulla Medical City, Arabian Gulf University, Manama 26671, Manama, Bahrain

**Nermin Kamal Saeed,** Medical Microbiology Section, Pathology Department, Salmaniya Medical Complex , Ministry of Health, Kingdom of Bahrain , Manama 12, Manama, Bahrain

**Nermin Kamal Saeed,** Microbiology Section, Pathology Department, Irish Royal College of Surgeon, Bahrain, Busaiteen 15503, Muharraq, Bahrain

**Corresponding author:** Mohammed Al-Biltagi, MBChB, MD, MSc, PhD, Chairman, Professor, Department of Pediatrics, Faculty of Medicine, Tanta University, Al Bahr street, Tanta 31511, Algharbia, Egypt. mbelrem@hotmail.com

## Abstract

For many years, ultrasound was thought to have no indications in pulmonary imaging because lungs are filled with air, creating no acoustic mismatch, as encountered by ultrasound wave beam. Lung ultrasound (LUS) was started in adult critical care settings to detect pleural effusion and acquired more indications over time. In the neonatal intensive care unit (NICU), the use of chest ultrasound has gained more attention during the last two decades. Being a radiation-free, bedside, rapid, and handy tool, LUS started to replace chest X-rays in NICU. Using LUS depends upon understanding the nature of normal lungs and the changes induced by different diseases. With the help of LUS, an experienced neonatologist can detect many of the respiratory problems so fast that interventional therapy can be introduced as early as possible. LUS can diagnose pleural effusion, pneumothorax, pneumonia, transient tachypnoea of the newborn, respiratory distress syndrome, pulmonary atelectasis, meconium aspiration syndrome, bronchopulmonary dysplasia, and some other disorders with very high accuracy. LUS will be helpful in initial diagnosis, follow-up, and predicting

the need for further procedures such as mechanical ventilation, diuretic therapy, surfactant therapy, *etc.* There are some limitations to using LUS in some respiratory disorders such as bullae, interstitial emphysema, and other conditions. This review will highlight the importance of LUS, its uses, and limitations.

**Key Words:** Lung ultrasound; Neonatal respiratory Disorders; Neonatal chest ultrasound; Meconium; Pneumonia; Pneumothorax



**Core Tip:** Lung ultrasound is a valuable imaging procedure in neonatal respiratory care. It helps diagnose many respiratory disorders with excellent accuracy and safety. Some limitations are experienced for its use, but its benefits are more.

**Citation:** Bediwy AS, Al-Biltagi M, Nazeer JA, Saeed NK. Chest ultrasound in neonates: What neonatologists should know. *Artif Intell Med Imaging* 2022; 3(1): 8-20
**URL:** https://www.wjgnet.com/2644-3260/full/v3/i1/8.htm
**DOI:** https://dx.doi.org/10.35711/aimi.v3.i1.8

## INTRODUCTION

Lung diseases are the most common reasons of respiratory distress in newborn, leading in some instances to respiratory failure; even may end with death. Mortality caused by neonatal respiratory problems was estimated to be 11% in the United States and 32% in China[1,2]. Thus, neonatologists need to identify the etiology and pathology of lung disease causing respiratory problems. Since the sixties of the last century, applying point-of-care ultrasound (POCUS) in neonates was first illustrated, with growing interest with several applications to be used over the past two decades[3,4]. Lung ultrasound started in adult critical care medicine to diagnose various lung and pleural problems. Then in the early nineties, chest ultrasound was suggested to diagnose neonatal respiratory distress syndrome (RDS). Since then, pediatric and neonatal ultrasound of the lung has developed rapidly[5]. After that, several indications were introduced for the lung ultrasound in neonates as transient tachypnoea of the newborn (TTN), neonatal pneumonia, pneumothorax, and meconium aspiration syndrome (MAS) with high specificity and sensitivity[6-10]. Neonatal lung ultrasound (LUS) is an easy bedside procedure with no radiation exposure and can be done serially in neonates[11,12]. LUS can differentiate neonatal respiratory diseases and predict neonatal morbidity[3]. Because of its advantages, LUS aids in distinguishing the various causes of neonatal respiratory failure and guides the management[3,13]. Another advantage of performing LUS in the neonatal intensive care unit (ICU) is the immediate interpretation by the neonatologist with a more accurate diagnosis aiding to start a precise and rapid therapeutic intervention[13]. Although the European Resuscitation Council guidelines recommend utilizing LUS to confirm the placement of the endotracheal tube (ETT) diagnose cardiac tamponade, pneumothorax, and pneumonia, the use of LUS is still not routinely taught in neonatology training programs around the world[14].

There was a notable increase in publications on the use of LUS in both adults and neonates during the last fifteen years. The successful establishment of LUS programs in some neonatal intensive care units (NICU) resulted in a significant reduction in chest radiograms and, subsequently, radiation exposure to patients[12]. One study showed that the risk of cancer occurrence in infants receiving a single small dose of radiation was two to three times higher than the average population and was six to nine times higher than the risk from an exposure of a 60-year-old patient[15]. The POCUS Working Group of the European Society of Paediatric and Neonatal Intensive Care issued evidence-based guidelines on POCUS for neonates and children in 2020[16]. Because it costs less than chest radiology, being radiation-free with higher sensitivity for diagnosing small lesions close to the pleural surface, LUS has been widely used in NICUs. Recently, it has been the most preferred radiological intervention for diagnosing many diseases in the neonatal ICU as RDS, TTN, pneumothorax, MAS, pleural effusions, and neonatal pneumonia than the chest X-ray[17]. LUS is beneficial in the initial diagnosis, follow-up, and assessing the need for further procedures such as mechanical ventilation. Every neonatologist needs to know LUS and get training courses for this unique safe technique.

## TECHNIQUE OF LUNG ULTRASOUND

Ultrasound imaging uses one principle; an interface reflects the ultrasound wave between the different media with various acoustic absorption and impedance[18]. Ultrasound is of limited use in normal well-aerated lungs as there is no acoustic discrepancy in the ultrasound beam as it confronts air[19]. LUS is very useful in neonates because of the thin chest wall and less ossification of the bony thoracic cage[11,20]. A high-frequency linear probe is preferred to perform LUS in neonates because of the relatively thinner chest walls and smaller thoraxes. This high-frequency probe gives a better image quality and allows visualization of the entire lung surface[21]. The high-frequency probe gives a good resolution with penetration to a superficial depth. We use probes with higher frequencies in preterm neonates, for example micro-linear probes with a small footprint (like a hockey stick). An operator with high experience may use different probe types[22]. Different ultrasound modes can be used for LUS. 2-Dimensional brightness (B-mode) and motion (M-mode), and the color doppler to estimate blood flow [23].

To perform lung ultrasound in neonates we perform it in the lateral, supine, or prone position. Each chest side hemithorax is divided into three areas: Posterior, anterior, and lateral, by the posterior and anterior axillary lines. We can perform longitudinal and transverse scans in all areas to directly identify the ribs, subcutaneous tissue, pleural line, and recognize the lung sliding to indirectly assess the lung tissue[21]. To evaluate or interpret the LUS images, we should understand some terms such as pleural line, A-lines, B-lines, lung sliding and acoustic shadowing artifacts (rib shadow). The pleural line (Figure 1) represents the lung's outer surface, including the visceral and parietal pleura. The pleural line is a regular and smooth hyperechoic line, moving to and fro with respiration. We can clearly visualize the pleural lines in neonates even without pleural or pulmonary pathology. It becomes apparent after birth following the first few breaths[24]. The Bat sign (Figure 2) represents a normal lung surface and is identified by visualizing the bright lateral pleural line (visceral and parietal) and the dark "bat wings" of the two adjacent ribs on each side. In the presence of lung or pleural diseases, the pleural line may become thick and coarse compared to the thin and regular hyperechoic pleural line shape in the healthy lung.

The A-lines are a group of parallel flat lines, occurring at regular distances below and in parallel with the pleural line. They represent a significant alteration in acoustic impedance at the pleuropulmonary line creating horizontal artifacts[25]. A-lines are echo artifacts reflected from the pleural line. They are visualized as hyperechoic, horizontal lines, occurring at equal spaces and extending deeply into the two-Dimensional image. The acoustic shadowing of the ribs represents an artifact arising from the ribs, shown by an anechoic area underneath the ribs and extending deeply into the two-dimensional image and disrupting the A-lines[26]. When the air content of the lung decreases as in subpleural interstitial edema, there will be an acoustic mismatch generated by the ultrasound wave between the fluid interface surrounded by air. This change will be reflected repeatedly at the deeper zones[21,27] and creates vertical artifacts called B-lines. These B-lines correlate with the pulmonary interstitial fluid content. The number of these lines increases with reducing the air content. B-lines or comet tail artifacts represent reverberation artifacts that are laser-like, hyperechoic, shadows that arise from this pleural line extending to the edge of the screen with coinciding movement with respiration. They can be caused by interstitial edema or interlobar septal pulmonary scarring[11,20]. The presence of multiple B-lines indicates alveolar interstitial edema[28,29]. Proof of compact coalesced B-lines in the lung denotes a serious form of the alveolar-interstitial syndrome, called "white lung". It is normal to visualize B-lines in healthy neonatal lungs. Their number will decrease with the baby's growth until being non-visualized at the age of 6 mo in a healthy infant[30,31]. Serial ultrasound imaging is advised to differentiate between standard B lines visualized during the neonatal period from pathological B-lines. If B lines increase, being more compact and coalesced, they will be more pathological. The denser the B-lines are, the more likely they are due to underlying lung pathology.

Lung sliding (Figure 3) represents the to-and-fro movement of the parietal and visceral pleura (pleural line) with respiratory movements and could be seen in B-mode and M-mode. Lung sliding visualized in B-mode is known as the movement of marching ants alongside the pleural line with respiration while, in M-mode, we can see lung sliding as the seashore sign in which the non-moving structures above the pleural line correspond to the sea, and the movement underneath the pleural line induces some irregularities simulating a sandy shore (Figure 4)[21,26]. Sometimes, the lung sliding is absent, which indicates a problem in the pleuropulmonary interface that can be observed in pneumothorax, complete atelectasis, pleuropulmonary pathology, and severe hyperinflation that could be seen in cases of foreign body aspiration[32]. Neonatal LUS scores provide a standardized approach to assess pulmonary pathology in the neonate, and evaluation of the disease progression is a semi-quantitative way[3,33-36]. Practically, the score of LUS is frequently assessed by six chest regions over the anterior and lateral zones of the chest. Early after birth, gravity plays a significant role, giving a slight distinction between the dependent and non-dependent lung zones[37]. For each zone, the score will range from 0 to 3. Thus, the total score will be between 0 and 18. Different neonatal pulmonary and pleural diseases have different numbers of B-lines and subpleural lung consolidations per each zone, which can help distinguish each of them[33]. A recent study proved that using more lung zones (10 or even 12 zones) in the first few days after birth did not result in better accuracy for diagnosis and management of

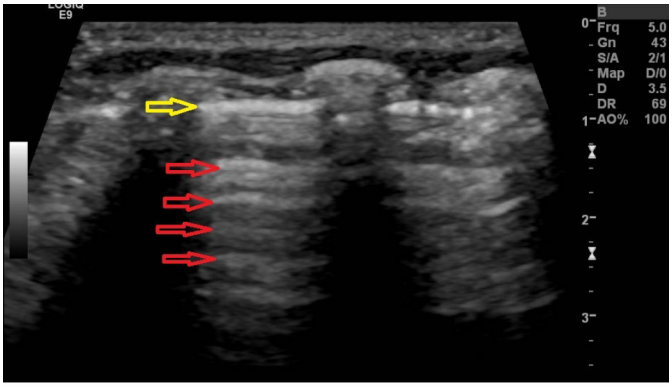


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**Figure 1 Pleural line and A-lines in normal lung.** The A-lines (red arrows) are horizontal artifactual repetitions of the pleural line (yellow lines) displayed at regular intervals.

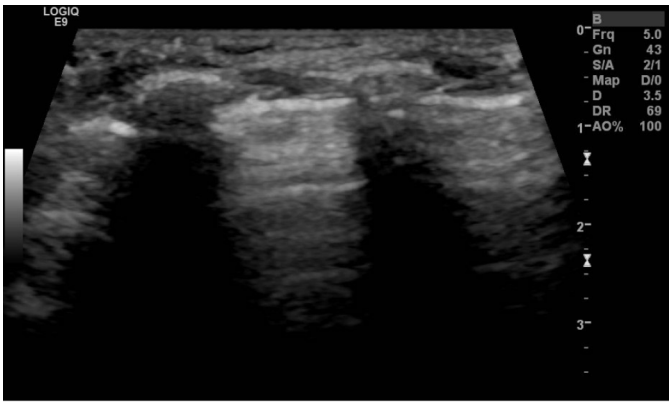


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**Figure 2 Bat sign created by the pleural line and ribs on either side.** This view represents a normal lung surface, where the bright lateral line is the visceral and parietal interface, and the dark "bat wings" are rib shadows.

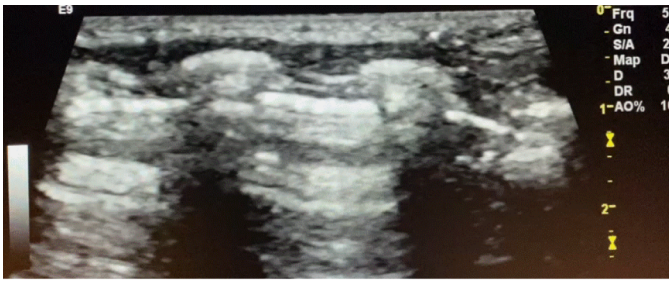


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**Figure 3 Lung sliding and a shimmering appearance of the pleura.** Lung sliding refers to a to-and-fro movement of the visceral pleura in contact with the parietal pleura due to shimmering/glimmering (or twinkling) of the pleural line on 2-Dimensional ultrasound.

bronchopulmonary dysplasia when compared to the standard six zones approach[38].

## CLINICAL USES OF NEONATAL LUS

Neonatal LUS has a broad spectrum of clinical uses nowadays. The guidelines made by the POCUS working group of the European Society of Paediatric and Neonatal Intensive Care in 2020[16] stated that there was reasonable evidence (level B evidence) for neonatal LUS use in cases of transient tachypnoea of the newborn (TTN), respiratory distress syndrome (RDS), pneumothorax, and pleural effusions (with the advantage of guiding the thoracentesis). In some other diseases, the level of evidence was less (level

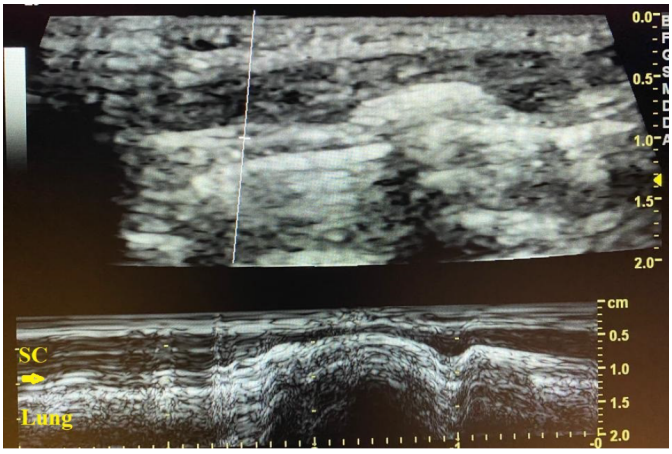


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**Figure 4 M-mode of the normal lung shows "Sand on the Beach" appearance or Seashore sign.** The movement of the lung during respiration creates a speckled appearance like grains of sand (the shore) beneath the bright pleural line (Yellow arrow). In contrast, the soft tissues (Subcutaneous fat tissues) above the pleural line do not move with respiration and do not change with time and thus have a linear appearance (Sea appearance).

C), such as pulmonary edema and atelectasis. Different algorithms were suggested for neonatal LUS, *e.g.*, evaluation of life-threatening situations[3,39], the neonatal respiratory pathologies algorithm [20], the neonatal LUS protocol[40,41], and SAFE-R protocol (which also include assessment of cardiac tamponade, myocardial function, pleural effusion, and pneumothorax) in the decompensating neonate [39]. These algorithms require more controlled studies on many patients with different pathologies. Some limitations for using LUS in neonates will be discussed separately.

## PLEURAL EFFUSION

LUS in the neonate can detect even small volumes of pleural effusion very efficiently and can be used to guide pleural fluid aspiration[42]. In the B-mode, fluid is usually anechoic, sometimes with hepatization of the lung parenchyma. We can see the sinusoid sign in-M mode with the visceral line moving towards the pleural line during respiration. Colour doppler is not commonly used in these cases but can differentiate between echogenic and solid collections inside the effusion[21,26].

## PNEUMONIA

*Pneumonia* is a severe neonatal disease that carries a high risk of morbidity and mortality, with about one million neonatal deaths yearly and about 10% of the worldwide child mortality[43]. Many pathogens are causing pneumonia in the neonates, such as bacteria, fungi, and viruses. Pneumonia can be acquired after birth or even during the intrauterine period[44]. The pathology includes epithelial injury of airways and alveoli, leakage of protein fluid (exudate), and interstitial edema of the alveoli. Clinical presentations are usually nonspecific and can be indistinguishable from RDS or TTN. Besides the laboratory workup, LUS can help in diagnosis. LUS in neonatal pneumonia cases shows pulmonary consolidation areas with irregular margins surrounding multiple B-lines. Other LUS findings that could present in pneumonia include an invisible pleural line on the affected part of the lung and absent lung sliding. Sometimes we can observe a dynamic air bronchogram, moving with respiration (Figure 5), especially in extensive areas of consolidation, which indicates the patency of airways (thus excluding atelectasis)[45]. In one study on forty cases of neonatal pneumonia *vs* forty neonates without pulmonary diseases, the authors found that LUS was a reliable method to diagnose neonatal pneumonia. They recommended routine use of LUS in the NICU[46]. A meta-analysis reviewed eight studies found that LUS has excellent sensitivity (96%) and specificity (93%) for the diagnosis of pneumonia in children, and the study recommended LUS as an alternative tool in such cases with no radiation exposure[47].

## RDS

RDS or hyaline membrane disease is a significant reason for NICU admission and neonatal death. It primarily happens in preterm babies as about 70% of cases are seen in neonates born before 28 wk of

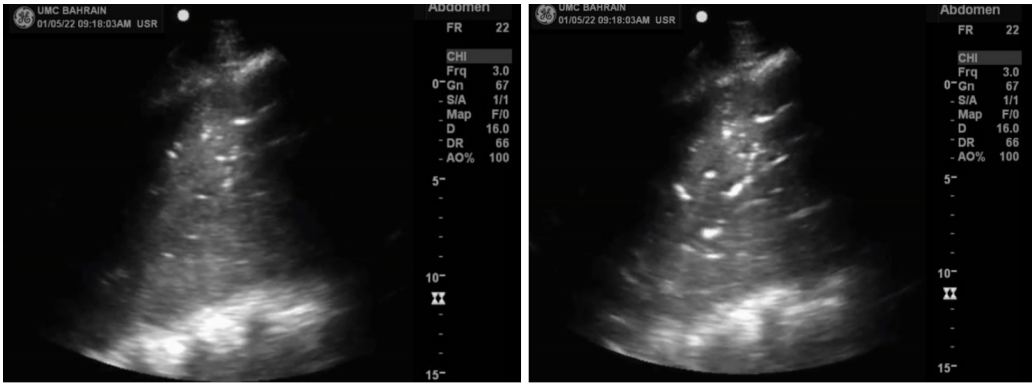


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**Figure 5 Dynamic air bronchogram.**

pregnancy, and 15%-30% of cases occur in neonates 32-36 wk of gestation[48]. Pulmonary surfactant deficiency is significant in the pathogenesis of RDS. Type II pneumocytes produce pulmonary surfactants. One of their essential functions is to reduce the surface tension in the alveoli preventing the end-expiratory collapse of the alveoli, which requires more work of breathing to re-open in the next respiratory cycle. Affected patients present with respiratory distress and failure within 4-6 h postpartum and, in many cases, require mechanical ventilation[21,26]. LUS in RDS cases shows compact B-lines that coalesce together, giving the appearance of an echographic white lung, a thickened and irregular pleural line, and multiple areas of subpleural pulmonary consolidation (reflecting the presence of alveolar collapse). In one study, these ultrasonic features showed both sensitivity and specificity of 100% for RDS diagnosis[49]. In another study involving 59 neonates having clinical features suggestive of RDS, only 23 of them had actual RDS. In that study, the sensitivity of LUS was 95.6% (in comparison to 91.3 for chest X-ray), and the specificity was 94.4% (it was 84.2% in chest X-ray)[50]. LUS appearance of RDS is, sometimes, not symmetrical in the same or both lungs. Due to gravity issues, these features are usually found in the posterior parts of the chest because of the supine position acquired by the baby most of the time. So, it is crucial to examine the posterior chest in neonates not to miss these signs[51].

The treatment of choice in cases of RDS is the administration of surfactant and supported ventilation as needed. Neonatal LUS is able to expect the requirement for giving surfactant therapy and possibility of mechanical ventilation. One study showed that the presence of white lung signs in neonatal respiratory distress anticipated the need for intubation and mechanical ventilation with good sensitivity and specificity (88.9%, 100%, respectively)[52]. Another study showed that the lung ultrasound score in the first few hours after birth significantly correlates with the oxygenation condition (oxygen indices) in neonates and revealed adequate reliability to predict the requirement for surfactant therapy in premature infants[37]. Two more studies showed that the accuracy of LUS was higher than the fraction of inspired oxygen ($FiO_2$) in predicting the need for surfactant administration in premature babies[53,54]. A recently published trial showed a significant ability of LUS in predicting the need for surfactant compared to $FiO_2$ as a guide for that[55]. The concept of Echography-guided Surfactant THERapy, which uses the LUS score to direct surfactant therapy, resulted in an earlier intake of surfactant, which reduced the duration of invasive mechanical ventilation without any additional cost[56-58].

## ATELECTASIS

*Atelectasis* is a collapse of a part of the lung parenchyma causing impairment of gas exchange. It can be caused by either airway obstruction, lung compression (by pulmonary or extrapulmonary lesion), or alveolar collapse due to increased surface tension of the alveolar wall. The most common mechanism of atelectasis in neonates is airway obstruction by thick mucus, meconium, or foreign particles. Atelectasis is usually associated with some other respiratory disorders[59]. Additionally, right upper lobe collapse in an intubated and mechanically ventilated baby can occur because of traumatic damage to the airway mucosa of the right-sided bronchi[60].

LUS can demonstrate atelectasis as an area of consolidation with the anechoic border and A-lines disruption[20,61]. Complete collapse leads to the absence of lung sliding and lung hepatization[11,61]. In severe atelectasis, lung pulse signs can be noticed in LUS, in which the collapsed part of the lung is pulsating with heartbeats[61]. Static air bronchogram can be observed with atelectasis, and this is different from dynamic air bronchograms (in pneumonia) that move with respiration, although differentiating between them is often challenging and requires an experienced sonographer[46,62]. Also, atelectasis in many cases is indistinguishable from pleural effusion in chest X-ray, but with LUS, it is easy to distinguish. One study showed that the sensitivity of LUS for diagnosing lung atelectasis was

100% *vs* 75% of chest X-rays (CT was the reference procedure in this study)[61]. Another study showed that the accuracy of LUS for diagnosis of post-anesthesia atelectasis in children was 88%, with a sensitivity of 89% and specificity of 88% (using magnetic resonance imaging as reference)[63].

## PNEUMOTHORAX

The incidence of pneumothorax in neonates is about 1%-2%, but this rate is much more in neonates on mechanical ventilation, reaching up to 30%[64]. Tension pneumothorax is mainly encountered in neonates on mechanical ventilation either due to the original disease (as meconium aspiration or ball-valve obstruction of airways causing air trapping and rupture of alveoli) or due to iatrogenic causes such as birth trauma or improper suctioning techniques[65]. LUS signs of a pneumothorax include absent lung sliding, absent B-lines, and the existence of lung point. The absence of lung sliding and B-lines can be explained by accumulation of air in the pleural cavity, preventing the movement of the visceral pleura. It is worth noting that any disease that interrupts the visceral and parietal pleural interface will also cause absent lung sliding. The lung point sign is an area identified where parietal and visceral pleura separate[66]. This sign may be lacking in large tension pneumothorax[67,68].

Many studies showed the usefulness of LUS to detect pneumothorax. One study showed sensitivity and specificity to be 96.7% and 100%, respectively[69]. Another study showed the superiority of LUS over chest X-rays in diagnosing pneumothorax[66]. Another large multi-center study found that LUS is a safe and effective tool to identify serious pneumothorax and assist to manage chest drainage without doing chest X-rays. That study also showed that LUS has sensitivity, specificity, positive predictive value, and negative predictive value reaching up to 100% in diagnosing pneumothorax[8]. Another study compared three imaging techniques for the diagnosis of pneumothorax. It showed that LUS had 100% sensitivity and specificity, chest X-ray had 96% sensitivity and 100% specificity, while chest transillumination had 87% sensitivity and 96% specificity[67].

## TTN

TTN, or the so-called "wet lung", is considered the most common reason of neonatal respiratory distress. TTN is usually a mild disorder, caused by a delay in the fetal lung fluid clearance (most of the fluid is removed by vaginal squeezing of the chest during labor, while the lymphatics system and pulmonary circulation clear the remaining fluid after being transported to lung interstitium)[70]. So, prematurity and elective cesarean sections are the main precipitating factors[72]. The condition usually resolves spontaneously within 24 h after birth but in a few cases may persist for several days. LUS can distinguish TTN from RDS by identifying B-lines' number and site[6,7]. In TTN cases, there are bilateral symmetric B-lines with a regular pleural line. Severe TTN presents as a white lung. LUS has high specificity but low sensitivity for the diagnosis of TTN. The double lung point sign represents the area between the upper and lower lung zones at which we can distinguish spaced-out B-lines next to confluent B-lines. So, double lung point can be considered a demarcation point of echogenic differences in the lung field[6,7,68].

The double lung point additionally occurs during the diseases recovery phase, such as severe TTN, RDS, and pneumonia[6] Sometimes a mixed RDS/TTN pattern can be identified when the baby has reduced reabsorption of the lung fluid and relative surfactant deficiency. This pattern can be recognized using the LUS score[72]. One prospective cohort study on 59 neonates with respiratory distress found that sensitivity and specificity of LUS for TTN diagnosis were 93.3% and 96.5%, respectively. These values were better than those observed in chest X-rays (89.4% and 91.3%, respectively)[50]. Another recent meta-analysis concluded that LUS has excellent specificity and sensitivity for diagnosing TTN [73]. Studies also showed that LUS could diagnose TTN and predict which neonate may need a higher level of care[74].

## BRONCHOPULMONARY DYSPLASIA

Bronchopulmonary dysplasia (BPD) is a common complication related to prematurity and is one of the common complications of RDS. BPD is associated with required respiratory support and/or oxygen supplement at 36 wk corrected gestation. It associates with long-term morbidity and even mortality in some cases[75]. In BPD, structural lung abnormalities, immature biochemical pathways, and oxidant injuries are associated with repeated pulmonary infections and poor nutrition, leading to impaired cardiopulmonary function[76]. LUS features of BPD include thickened coarse pleural lines, subpleural consolidations, and B-lines. According to the severity of inter-lobar septal scarring and interstitial edema, B-lines can be scattered or diffuse. LUS score can help diagnose BPD severity[77] and guide the management, including diuretics use[36].

LUS score can predict the development of BPD in some studies. In a multi-center cohort study, authors found that LUS score on day seven and day fourteen correlates with the oxygenation indices and predicts BPD occurrence when adjusted for gestation and sex[38]. In another cohort study, LUS was done on days 3, 7, and 14 in neonates born before 29 wk gestation[78]. This study showed that the LUS score was higher in neonates who later developed BPD on all-time points, with an LUS score of more than ten on day seven having the highest sensitivity and specificity.

## MAS

MAS is due to intra-uterine aspiration of meconium-contaminated amniotic fluid into the newborn airways due to fetal hypoxia, acidosis, or infection[79]. Meconium obstructs the airways and induces surfactant dysfunction, chemical pneumonitis, and secondary infection. These will lead to hypoxia due to ventilation/perfusion mismatch[80]. Neonates with MAS have yellowish greenish (meconium stained) skin, umbilical cord, and nails, and signs of respiratory distress. It may develop immediately after birth. MAS is a specific type of pneumonia. So, its LUS features are like pneumonia, giving the features of irregular subpleural consolidations with coalescent B-lines. These features are usually unilateral[81]. Some studies showed the usefulness of LUS for diagnosing MAS in neonates[9,82]. However, LUS should be correlated to the clinical circumstances and physical examination.

Table 1 summarizes lung ultrasound appearance in different neonatal lung diseases compared to chest X-rays.

## OTHER USES OF LUNG ULTRASOUND IN NEONATES

LUS can be used to assess lung recruitment with positive end-expiratory pressure without the need for exposure to ionizing radiation by doing CT chest[83]. LUS can also effectively monitor bronchoalveolar lavage in neonates with atelectasis, with an efficacy approaching 93%[84]. Another application of interest that was seen in some studies is the use of LUS to assess the position of the ETT in the trachea by measuring the space between the ETT distal end and the aortic arch apex[85] or the space between ETT distal end and the superior edge of the right pulmonary artery[86]. We can achieve this technique by utilising either a phase array probe (while doing the high parasternal view) or a linear probe (in the midsagittal view). Another study reported the use of LUS to immediately confirm the proper ETT position during neonatal resuscitation. This study used a linear probe in the transverse position[87].

Another critical use of ultrasounds is evaluation of vocal cord function. One study displayed that utilising high-frequency linear hockey stick probe in a transverse position over the middle of the neck could identify the presence of vocal cord paresis post-operatively (after aortic arch repair) with high sensitivity and specificity is compared to flexible fibreoptic endoscopy[88]. LUS has also been utilized to evaluate the diaphragm[89,90]. A recent study used LUS and diaphragmatic shortening fraction, a known way of assessing adult diaphragm function, to evaluate diaphragm in neonates. This study found that the diaphragmatic shortening fraction could be assessed in neonates[91]. LUS has also been suggested as a modality to follow asymptomatic CPAMs, but more studies are needed to stabilize this indication[92,93].

## LIMITATIONS OF LUNG ULTRASOUND USE FOR NEONATAL RESPIRATORY PROBLEMS

Although LUS is a very effective and safe imaging technique in neonates, we should consider the clinical finding of each case. Moreover, according to the application of LUS, and some problems in actual clinical practice, LUS has some limitations in some pulmonary conditions. For example, as mentioned above, the diagnosis of CPAMs using LUS is still not standardized, and many studies must be done in this context. Some cases of CPAMs can be detected in utero using ultrasound as the fetal lung is filled with fluid. On the contrary, due to air-filled neonatal lungs, their diagnosis by LUS in the neonatal period seems to be difficult because these lesions are usually away from the chest wall. Thus, lesions that are located away from the pleura could not be visualized by LUS[92].

LUS cannot identify some specific lesions because of the influence of gas in front of the lesion. When the acoustic beam of ultrasound encounters gas, it will be reflected ultimately. So, cases of pulmonary bullae cannot be visualized by LUS because of the large amount of gas in the bulla reflecting the acoustic beam of ultrasound. Similarly, the presence of subcutaneous emphysema or pneumomediastinum will affect the results of LUS due to the same reasons described above. Although LUS is a handy tool to diagnose pneumothorax, it cannot measure the size due to the total reflection caused by the gas[66].

**Table 1 Lung ultrasound appearance in different neonatal lung diseases compared to chest X-ray**

| Disease | Chest X-ray | Lung ultrasound |
|---|---|---|
| Pleural effusion | Homogenous opacity obliterating costophrenic and cardiophrenic angles | B-mode: Fluid is anechoic, sometimes ± hepatization of the lung parenchyma. M-mode: The sinusoid sign with the visceral line moving towards the pleural line during respiration |
| Pneumonia | Homogeneous opacities that can be patchy or lobar in distribution | Consolidation areas with irregular margins surrounding multiple B-lines. Invisible pleural line on the affected area. Sometimes: Dynamic air bronchogram |
| RDS | Alveolar shadowing (ground glass) with air bronchogram | Compact coalescent B-lines (white lung). Thickened, irregular pleural line. Multiple areas of sub-pleural consolidation |
| Atelectasis | Area of opacity in the lung with features of volume loss as shifting of mediastinum to the same side, pulled fissure, *etc.* | Area of consolidation with anechoic clear border and disrupted A-lines. Static air bronchogram. Complete collapse leads to the absence of lung sliding, lung hepatization, and lung pulse signs |
| Pneumothorax | Jet black translucency with collapsed lung and sometimes mediastinal shift to the other side | Absent lung sliding, absent B-lines, and the presence of lung point |
| TTN | Interstitial oedema predominantly in the peri-hilar region (wet silhouette) | Double lung point sign. B-lines. In severe cases: (white lung) |
| BPD | Ill-defined diffuse reticular markings with circular lucent areas in between and hyperinflated lung | Thickened coarse pleural linesSubpleural areas of consolidation. B-lines |
| MAS | Patchy consolidation | Same as pneumonia |

BPD: Bronchopulmonary dysplasia; MAS: Meconium aspiration syndrome; RDS: respiratory distress syndrome; TTN: Transient tachypnoea of the newborn.

Consequently, we need more studies to quantify the size of pneumothorax using LUS. Pulmonary interstitial emphysema is another condition that LUS cannot diagnose. In a published case study, the authors used LUS to follow-up localized interstitial emphysema. The infant presented again with tachypnoea after being treated with continuous positive airway pressure for three days. The chest computed tomography revealed localized interstitial emphysema of the left upper lobe, whereas LUS did not show this lesion[94]. We emphasized that using LUS is potentially harmful without adequate expertise. It may not provide definite diagnostic information and may allow over trust in the procedure, which could have profound legal implications and not address the underlying lesions. The misuse of artifacts as a diagnostic tool should be abandoned. Lung ultrasound imaging is advantageous when definite imaging is possible, even in the newborn.

## CONCLUSION

*Lung ultrasound* is a valuable imaging tool frequently used in neonatal respiratory care. It helps diagnose many respiratory disorders with excellent accuracy and safety with no radiation risk. Lung ultrasound is operator dependent and needs adequate experience to achieve good results. Some limitations are encountered for its use, but its benefits are more.

## ACKNOWLEDGEMENTS

We thank the anonymous referees for their useful suggestions.

## FOOTNOTES

**Author contributions:** Bediwy AS, Al-Biltagi M, Nazeer JA, and Saeed NK collected the data and wrote and revised the manuscript.

**Conflict-of-interest statement:** The authors declare no conflicts of interest for this article.

**Country/Territory of origin:** Egypt

**ORCID number:** Adel Salah Bediwy 0000-0002-0281-0010; Mohammed Al-Biltagi 0000-0002-7761-9536; Jameel Ahmed Nazeer 0000-0002-0085-9822; Nermin Kamal Saeed 0000-0001-7875-8207.

**S-Editor:** Liu JH
**L-Editor:** A
**P-Editor:** Liu JH

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