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Lung Ultrasound in Prediction of Bronchopulmonary Dysplasia in Neonates

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Abstract

Hyaline membrane disease (HMD) is one of the most common causes of respiratory distress in premature neonates. The most serious complications of prematurity and associated HMD with neonatal mechanical ventilation is bronchopulmonary dysplasia (BPD) which characterized by chronic respiratory signs, persistent oxygen requirement, and an abnormal chest X-ray at 1 month of age postnatal or at 36 weeks corrected age. To determine the importance of lungs ultrasound (US) in prediction of BPD development in neonates with HMD and to detect the earliest neonatal age for BPD development diagnosis. A prospective descriptive study done on 85 preterm newborns with respiratory distress syndrome, admitted in neonatal intensive care unit (NICU) in El Galaa teaching hospital in Cairo, from November 2020 to March 2021. The study included: Preterm neonates (< 37 weeks gestation), having respiratory distress syndrome (RDS) whether mechanically ventilated or not with maternal history of antenatal corticosteroid administration. We excluded: Full term neonates, respiratory distress of causes other than respiratory distress syndrome, congenital anomalies, metabolic disorders or suspected inborn errors of metabolism and neurological causes leading to hyperventilation like seizures. The aim of first US examination is to determine RDS US pattern presence or absence. This was done initially on admission during the first 3 days of life. The subsequent examinations done twice weekly were for follow up. The US pattern correlated with the clinical and radiographic pattern of BPD at or after 28 days of life. Twenty (23.6%) preterm neonates developed BPD clinically and radiologically, they were 13(65%) males and 7(35%) females, with mean gestational age 32.3±2.2 weeks, whether they were mechanically ventilated or not. Nine (10.6%) preterm neonates died within the first three weeks of life, they were 5(55.5%) males and 4(44.5%) females with mean gestational age 31.6±2.1weeks. Ultrasound examination of the lung done in the period (9^{th}-13^{th} day postnatal) has a high predictive value for subsequent development of BPD. Lung US may be utilized in ventilated preterm neonates for early prediction of BPD in the period (9^{th}-13^{th} day postnatal) where persistence of the abnormal retro diaphragmatic hyper echogenicity by this time is a predictor for the future development of BPD**.**

Keywords: Neonates, RDS, BPD, Lung ultrasound.

1. Introduction

Bronchopulmonary dysplasia (BPD) is considered as a major morbidity for preterm neonates and associated with poor neurodevelopmental outcomes [1]. BPD

incidence has not decreased the past decade despite of neonatal care advances [2, 3]. Bronchopulmonary dysplasia (BPD) is characterized by chronic respiratory signs, persistent oxygen requirement, and an abnormal chest Xray at 1 month of age postnatal or at 36 weeks corrected age [4]. Bronchopulmonary dysplasia (BPD) is a chronic lung disease occurs in premature neonates managed by mechanical ventilation for a primary lung disease [5]. Bronchopulmonary Dysplasia Pathogenesis is caused by Acute lung injury which is due to oxygen toxicity, volutrauma and barotraumas from mechanical ventilation. Interstitial and cellular injury leads to the release of proinflammatory cytokines (IL-6, IL-8, interleukin 1B, tumor necrosis factor) causing secondary alveolar permeability changes and recruiting inflammatory cells into alveolar spaces and interstitium [6]. Fibrosis and cellular hyperplasia which may change interstitium due to the release of growth factors and cytokines, leading insufficient repair is the Chronic phase of lung injury [6].

Chest transthoracic ultrasound (US) can be used in the evaluation of parenchymal, pleural, and chest wall diseases [7].

Normal pattern is consisted of normal echo complex of the diaphragm with no hyper echogenicity retro diaphragmatic. Hyaline membrane disease (HMD) pattern is consisted of diffuse hyper echogenicity retro diaphragmatic. replacing the normal echo complex diaphragm [8,9]. BPD pattern: Similar to the same hyper echogenicity as HMD pattern, but less homogeneous and less diffuse [10].

The aim of the study determines the importance of lungs ultrasound (US) in prediction of BPD development in neonates with HMD and to detect the earliest neonatal age for BPD development diagnosis.

2 .Patients and Methods

A prospective descriptive study done on 85 preterm newborns with respiratory distress syndrome, admitted in neonatal intensive care unit (NICU) in El Galaa teaching hospital in Cairo, from November 2020 to March 2021.

These preterm neonates under study were followed up during their neonatal period (1st 28 days of life) for possible prediction of future development of bronchopulmonary dysplasia by lung ultrasound. The study included: Preterm neonates (< 37 weeks gestation), having respiratory distress syndrome (RDS). We excluded: Full term neonates, respiratory distress of causes other than respiratory distress syndrome, congenital anomalies, metabolic disorders or suspected inborn errors of metabolism and neurological causes leading to hyperventilation like seizures.

2.1 Each of the preterm neonates included in the study was subjected to the following

1. Full clinical history& examination.
2. Laboratory investigations.

3. Radiological investigations**:** Chest x-ray was done initially within first 24 hours of life, then twice weekly for follow up (8 x-rays) and diagnosis of BPD, where staging of BPD was done into four stages according to severity of x-ray findings.

4. Chest ultrasound was done using a Toshiba US machine with a 6.5MHz curvilinear probe. Excellent resolution and adequate penetration were given by high frequency probe. To obtain hard copy images a Sony black and white printer was used. We do chest ultrasound by the same method as described by Avni et al (**12**). Beneath the inferior end of the rib cage Sagittal trans-hepatic scanning was done, scanning superiorly to visualize the lung base. On the left side using the spleen the same was done.

5. The first US examination was done to determine RDS US features which is diffuse retro-hepatic and retro-splenic hyper-echogenicity replacing the normal echo-pattern of diaphragm, and estimation of RDS severity according to Bober & Swietlinski [12] Staging. This was done initially on admission during the first 3 days of life. The subsequent examinations done twice weekly were for follow the evolution of the reterodiaphragmatic appearance.

6. A BPD ultrasound pattern can be diagnosed when the hyperechogenicity seen by ultrasound in cases of RDS partially resolved, appearing on follow up evaluation less homogenous and less extensive. The diaphragm is not clearly visualized and there is in the area behind the full extent of the diaphragm a sharply hyper echoic line with sharp hyper echoic eventration artifact replacing the diaphragm, with persistence of the hyperechogenicity with interspersed normal areas in-between with irregular hyperechogenicity in BPD [12].

7. Stages of RDS severity by ultrasound scale includes that Stage I showed Retro phrenic striped pattern of diverging radially, hyperechogenicity observed only on expiration. Stage II showed Retro phrenic striped pattern of diverging radially, hyperechogenicity observed only during inspiration, and merging together to form areas of homogenous echo enhancement on expiration. Stage III Retro phrenic homogenous hyperechogenicity observed irrespective of respiratory phase [9].

8. The final ultrasound pattern was correlated with the clinical and radiographic features of BPD at or after 28 days of life. Clinical resolution of RDS includes improvement of respiratory distress clinically.

2.2 Statistical analysis

Statistical analysis was performed using statistical software SPSS (Statistical Package for Social Science) version 12. Descriptive statistics for the group of the studied neonates were calculated where mean and standard deviation used to express numerical data; frequency and percentage used to express qualitative data.

3. Result

The present study included 85 preterm newborns (47 males & 38 females, mean gestational age was 33.4weeks) admitted in NICU of El Galaa Teaching Hospital because of Respiratory distress syndrome (RDS) diagnosed clinically and radiological. According to their fate the total number under study was subdivided into two groups:

Group (Resolved RDS)*:* Fifty-six preterm neonates resolved from RDS (65.8%), they were 29(50.2%) males and 27(49.8%) females, with mean gestational age 34.2±1.5 weeks, they have maternal history of antenatal steroid, they are whether mechanical ventilated or not and they were discharged in fair general and ventilation conditions and

Group 2(BPD)*:* Twenty (23.6%) preterm neonates developed BPD clinically and radiologically, they were 13(65%) males and 7(35%) females, with mean gestational age 32.3±2.2 weeks, they have maternal history of antenatal steroid, also they were mechanically ventilated, ventilator settings of Resolved RDS (gp1) and BPD (gp2) showed high statistically significant increase in FiO2 in BPD neonates.

Nine (10.6%) preterm neonates died within the first three weeks of life due to neonatal sepsis, they were 5(55.5%) males and 4(44.5%) females with mean gestational age 31.6±2.1weeks.

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Table (1): Comparison between studied groups as regards clinical data.

Compared Group	GA	Wt.	HR median	RR median median
RDS (N.56) (Gp.1) Mean ±SD	34.21 1.52	2.39 0.51	130	62
BPD (N.20) (Gp.2) Mean ±SD	32.26 2.23	1.89 0.91	129	71
T	-2.99	-2.19	-.052	5.28
P	.004*	.005*	.952	0.000**

Table (2): Statistical comparison between ventilator settings of Resolved RDS (gp1) and BPD (gp2).

Compared group	PIP	PEEP	Ventilator Rate	Flow	IT	FiO2
Resolved RDS Mean ±SD	21.6 2.97	4	51.88 10.67	6.44 .88	0.39 0.02	0.57 0.16
BPD Mean ±SD	22.62 1.89	4	56.54 4.27	6.92 1.04	0.4 0.0	0.77 0.12
T	0.94		1.42	1.13	1.35	3.37
P	0.36		.172	.259	0.188	0.003**

Table (3): Ultrasound predictive values per days tested.

Days of US test	*Sensitivity%*	*Specificity%*	*PPV%*	*NPV%*
1st -3rd	80.0	0	78.0	0
9th - 13th	100	79.0	83.0	100
19th - 23rd	87.0	40.0	82.0	50.0

GA: gestational age; Wt: weight; HR: heart rate; RR: respiratory rate. Table. 1 shows statistically significant decrease in gestational age, & weight in BPD group, there was high statistically significant increase in respiratory rate in BPD group. $p<0.05$= significant * PIP= peak inspiratory pressure, PEEP= positive end expiratory pressure, IT =inspiratory time, FiO2=fractional inspired oxygen concentration. Table. 2 shows high statistically significant increase in FiO2 in BPD neonates. Measuring the accuracy of diagnostic procedures was done using sensitivity and specificity to revise probabilities and depend on performing calculations of various threshold periods; ultrasound examination of the lung done in the period (9^{th}-13^{th} day) has a high predictive value for subsequent development of BPD. PPV = positive predictive value, NPV = negative predictive value.

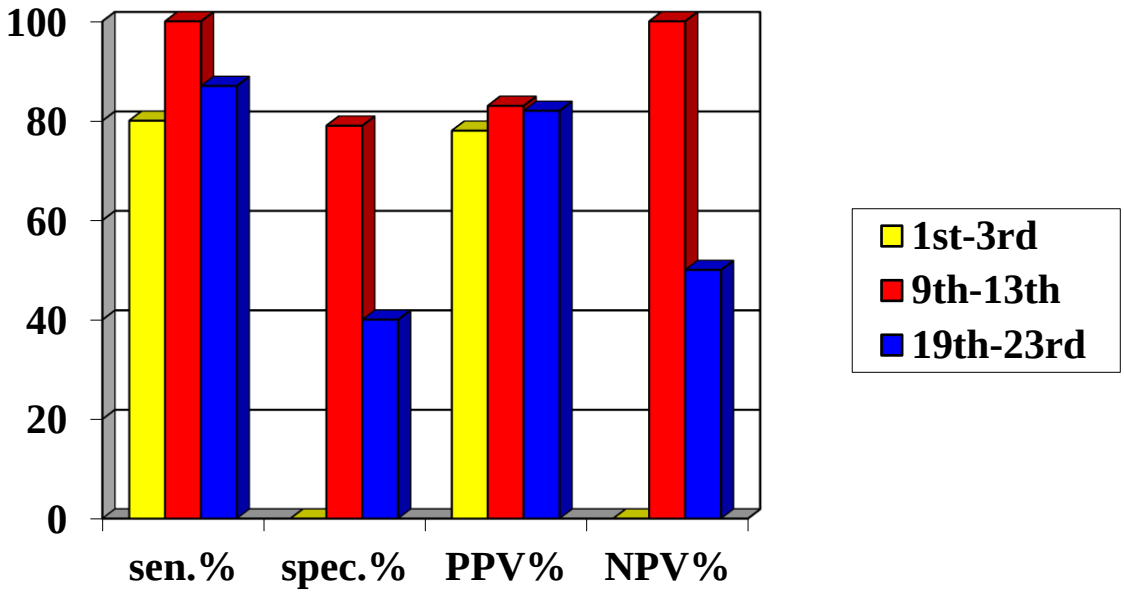


Figure (1): Measuring the accuracy of chest ultrasound in prediction of BPD.

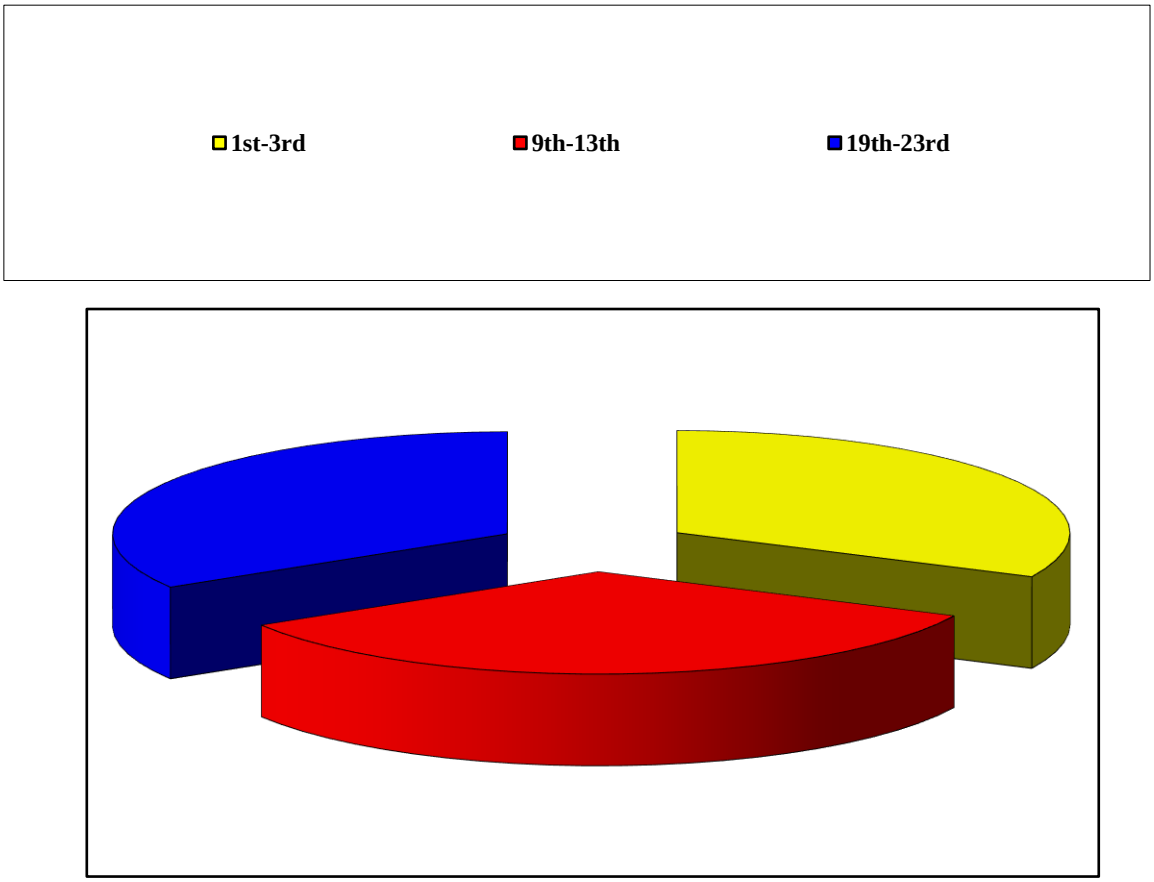


Figure (2): Predictive values of ultrasound per days tested.

Table .3 shows that persistence of abnormal ultrasonographic findings of BPD at the time span from 9th -13th day of life with the highest predictive values. Figures .1 and 2 show that the ultrasound is highly predictive for the development of BPD in the age 9^{th}-13^{th} of life.

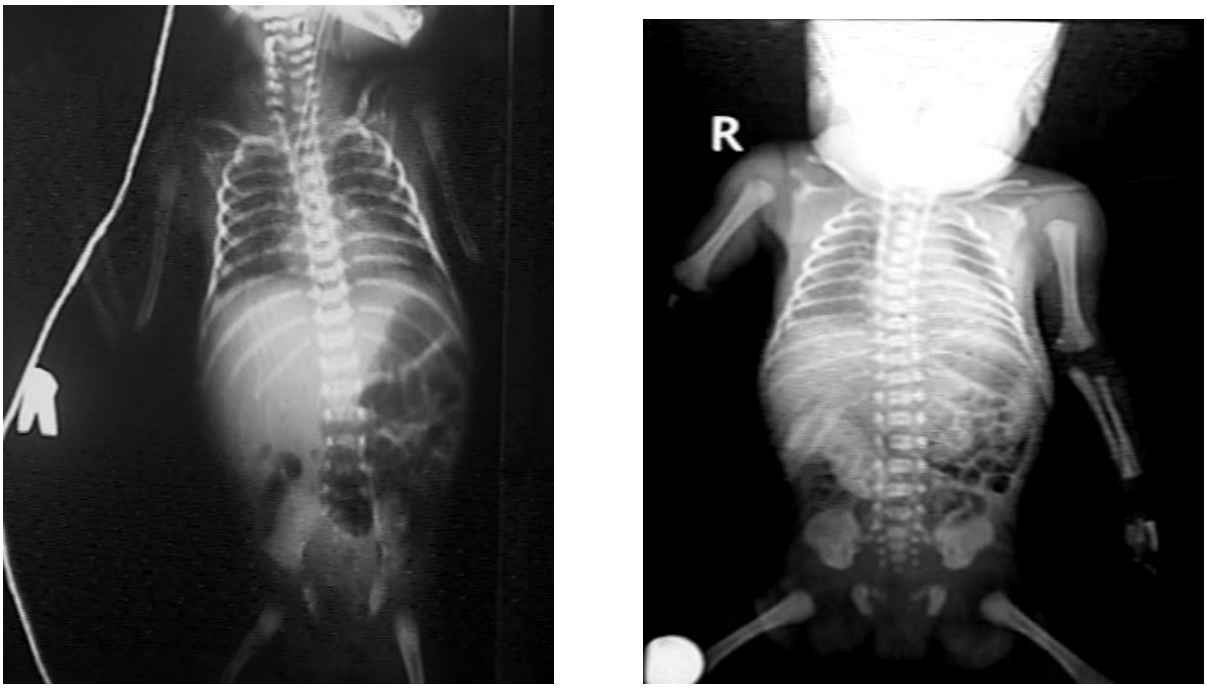
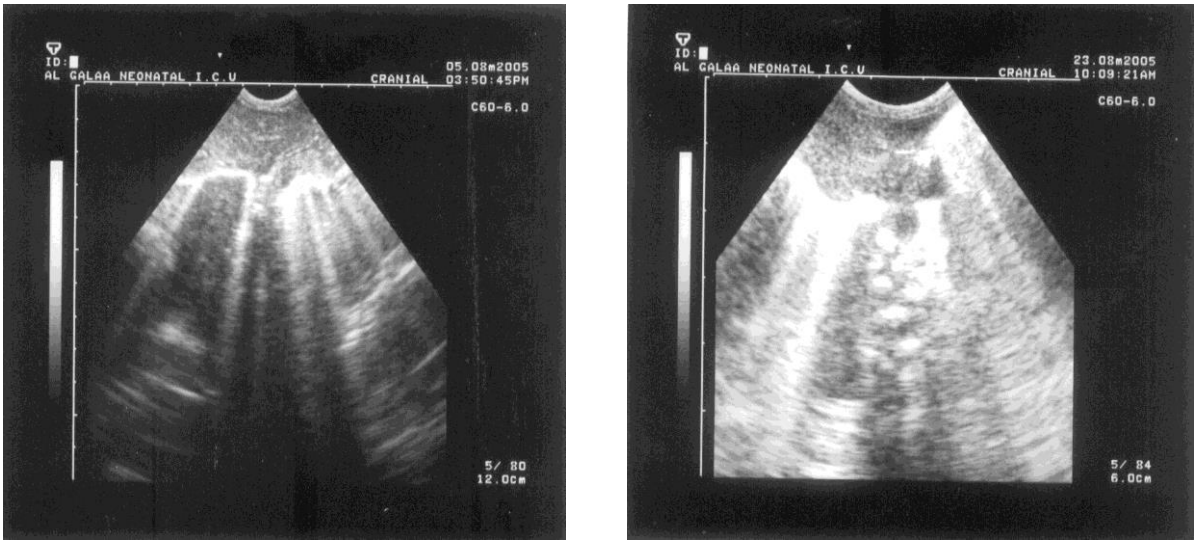


Figure (3): Case 22: A male preterm neonate 33 weeks gestation with grade 1 RDS, the x-ray shows fine reticulogranular mottling & good lung expansion. The second x-ray shows the baby after development of BPD with diffuse reticulogranularity.



RDS **BPD**

Figure (4): Case 22: A male preterm neonate, 33 weeks, with grade 1 RDS showing (a)reterophrenic striped pattern of hyperecchogenicity diverging radially, observed only on expiration., (b) the second ultrasound was after development of BPD showing hypereccogenicuty seen by ultrasound in cases of RDS only resolved partially on follow up evaluation appearing less homogenous and less extensive. The diaphragm is not clearly visualized and is replaced by hyper echoic line with hyper echoic reventration artifact filling the area behind the diaphragm, with persistence of the hypereccogenicity with interspersed normal areas in-between with irregular hypereccogenicity in BPD.

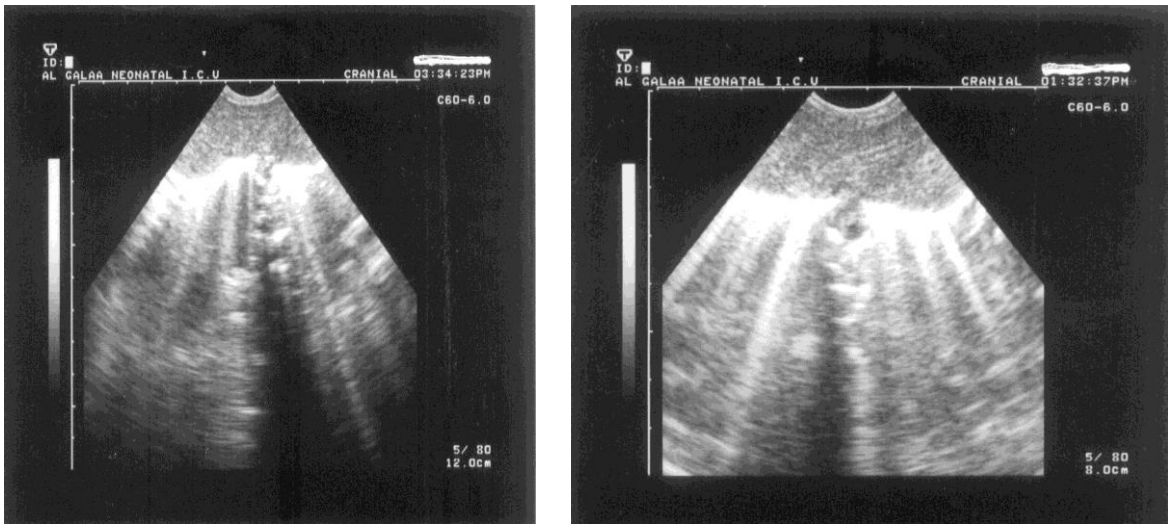


Figure (5): Case 22: A male preterm neonate, 33 weeks, with grade 1 RDS showing (a)reterophrenic striped pattern of hyperecchogenicity diverging radially, observed only on expiration., (b) the second ultrasound was after development of BPD showing hypereccogenicuty seen by ultrasound in cases of RDS only resolved partially on follow up evaluation appearing less homogenous and less extensive. The diaphragm is not clearly visualized and is replaced by hyper echoic line with hyper echoic reventration artifact filling the area behind the diaphragm, with persistence of the hypereccogenicity with interspersed normal areas in-between with irregular hypereccogenicity in BPD.

4. Discussion

One of the most common morbidities among premature infants is bronchopulmonary dysplasia where the developing lung injury is caused by interaction between a number of contributing factors and susceptible host [5].

The current study was based on the development of typical BPD that occurred in preterm neonates with respiratory distress syndrome. However, a different type of BPD has been reported which is the atypical type with no initial RDS, although BPD without preceding RDS is less common than that preceded with RDS, yet it comprises one-third of all cases of BPD. BPD without RDS is less severe in clinical characteristics and chronic oxygen requirements than that with RDS type [14].

In our study, the incidence of BPD was inversely proportionate to gestational age ($p<0.05$), with highest incidence from 31-34 weeks gestation. Hermensen and Lorah, [15] reported that BPD is most common neonates < 28 weeks' gestation and one third neonates at 28 to 34 weeks' gestation, but < 5% of neonates > 34 weeks' gestation. Choi et al. [12] reported that gestational age is a risk factor for the development of BPD. Morris et al. [16] reported that there was significant decreased incidence of BPD at 36 weeks gestation.

This study showed that birth weight of the group under study was significantly lower in the group that developed BPD ($P>0.05$). Ameenudeen et al. [17] found an increase in incidence of BPD with lower birth weight, Donaldsson et al. [18] & Gilfillan et al. [19] found that the highest incidence of BPD in their studies were in the group below 1Kg. Sharma et al. [20] reported that premature small for gestational age (SGA) neonates have significantly higher risk of developing BPD compared to premature adequate for gestational age (AGA) neonates. Reiss et al., [21] reported that SGA neonates < 32 weeks gestation were a high-risk group as regards pulmonary morbidity.

Ventilatory support is a risk factor of lung injury in preterm neonates. Nevertheless, when invasive forms of ventilatory support as intermittent mechanical ventilation is

used the incidence of BPD in neonates increases [22].

Lung and systemic inflammation are rapidly induced by mechanical ventilation. Mechanical ventilation in immature lung cause edema, hemorrhage, and epithelial necrosis, which inhibit surfactant function, compromise lung mechanics, and promote proinflammatory cytokines expression [23].

In the current study BPD was higher significantly with high FiO2 levels in the group who is mechanically ventilated ($p<0.05$), with no significant correlation with other ventilator parameters. Thus, oxygen toxicity is a contributory factor for the development of BPD. This agreed with Gilfillan et al. [19] who declared that high FiO2 levels >60% and mechanical ventilation in neonates with immature lungs are associated with a high incidence of BPD. But Apurwa et al. [24] reported that in preterm neonates with RDS, systemic inflammation, as detected by circulating phagocytes activation, starts within hours of mechanical ventilation onset, and it does not correlate with high FiO2 levels. They reported no such activation in preterm neonates without mechanical ventilation or in neonates managed by NCPAP; so, this activation may be induced by mechanical ventilation.

In the current study transabdominal ultrasound was done twice weekly, the first ultrasound done within the first three days of life showed radiological findings significant of different grades of RDS for all the neonates under study. Analysis of the results obtained in this study showed high sensitivity (80%) of ultrasound method in diagnosis of RDS in the first three days of life ,while 100% sensitivity in 9^{th} -13^{th} day of life, and 87% sensitivity on day 19^{th} -23^{rd} ,this result was consistent with results obtained by Bober & Swietliński [9] who found 100% sensitivity in ultrasound diagnosis of RDS in the first three days , and Pieper et al. [12] who found 80% sensitivity of ultrasound on day 3 of life while it became 100% on day 9 of life and 80% on day 14 of life and 70% day 19 of life .

Our study showed that there was a tendency of over diagnosis of RDS using ultrasonography in the second week of life (specificity 79%), but low specificity in the first week of life (0%) and 40% specificity on 19^{th} -23^{rd} days. This was against what Bober & Swietliński [9] found in the first week ultrasound diagnosis of RDS 92% specificity. But Pieper et al. [12] found lung ultrasound specificity on the third and ninth days of life 50%, and 53% specificity days 14 and 19 of life. As regards the ultrasound predictive value in BPD diagnosis, this study showed ultrasound positive predictive value (PPV) 78% in the 1^{st} - 3^{rd} days of life, it increased to 83% in the 9^{th} - 13^{th} days of life and decreased to 82%-day 19^{th} - 23^{rd} of life. Pieper et al. (2004) found PPV of ultrasound in predicting BPD 38% day 3 of life, 45% day 9 of life and 37% day 19 of life. In this study, depending on performing calculations for various threshold periods, ultrasound examination of the lung done in the period (9^{th}-13^{th} day) for subsequent presence of BPD has a high predictive value. Pieper et al. [12] concluded that lung ultrasound for BPD development prediction is a valuable method and they reported that lung ultrasound for subsequent BPD development on day 9 postnatal have the highest predictive value. Avni et al. [13] reported on prolonged presence beyond 7-10 days of ultrasound findings suggesting maintained lung pathology in the form of reterophrenic hyperechogenicity there is an increased incidence of BPD in these neonates. Copetti et al. [25] observed that at 36 weeks' gestation (post conception), the pleural line changes (irregular and thickened) and hypoechoic multiple subpleural areas are considered predictive for future development of BPD.

Copetti et al. [25] concluded that chest ultrasound has a great advantage in the preterm neonates because it can be done bedside, non-ionizing, can be done several

times without harm but it requires only alimentary skill.

5. Conclusion

Ultrasound chest examination showed high sensitivity in diagnosis of RDS in the first three days of life. US examination of the lung can be used routinely in ventilated preterm for follow up and early prediction of BPD by the 9^{th}- 13^{th} day, at which abnormal retro diaphragmatic hyperechogenicity persistence is a predictor for the future development of BPD.

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