Relationship between bronchopulmonary dysplasia phenotypes and clinical outcomes with HRCT score in preterm infants

Qiong Yao[1], Li-li He[1], and Xi-hong Hu[1]

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Abstract

Background: To assess the relationship between high-resolution computed tomography (HRCT) abnormalities with the clinical phenotypes and outcomes in preterm bronchopulmonary dysplasia (BPD) infants. Methods: Totally, 81 preterm infants were enrolled between 2013 and 2020. Clinical phenotypes of BPD mainly include BPD severity, pulmonary hypertension (PH), and large airway lesion (LAL). The outcomes included death before hospital discharge, home oxygen treatment, or home pulmonary vasodilator therapy, were assessed. Total scores (TS) of high-resolution CT (HRCT) were summed in every lobe in 7 aspects: hyperaeration score (HS), composing decreased attenuation, mosaic attenuation, and bulla/bleb; parenchyma score (PS), composing linear lesions, consolidation, bronchial wall thickening, and bronchiectasis. Results: TS (r=0.49), HS (r=0.31), PS (r=0.30), decreased attenuation (r=0.21), mosaic attenuation (r=0.31), bulla/Bleb (r=0.27) and linear densities (r=0.55) displayed a correlation with BPD severity. TS (r=0.28), PS (r=0.35), linear densities (r=0.34) and consolidation (r=0.24) displayed a correlation with PH. TS (OR 1.11, 95% CI 1.01-1.21), PS (OR 1.17, 95% CI 1.01-1.36) and linear densities (OR 2.23, 95% CI 1.34-3.71) was related to the composite outcomes. Linear densities (OR 2.30, 95% CI 0.96-5.49), TS (OR 1.16, 95% CI 1.01-1.33) and HS (OR 1.17, 95% CI 1.01-1.35) was associated with pulmonary vasodilator. Consolidation (OR 2.09, 95% CI 1.07-4.08) and PS (OR 1.27, 95% CI 1.00-1.60) was closely related to the death. Linear densities (OR 2.36, 95% CI 1.22-4.57, p=0.01) were risk factors of home oxygen therapy. Conclusions: HRCT scores were correlated with the BPD severity, PH and poor clinical outcome.

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Keywords: bronchopulmonary dysplasia, preterm infants, pulmonary hypertension, tracheomalacia, computed tomography

Introduction

Bronchopulmonary dysplasia (BPD) is a common respiratory complication manifested in approximately 40% of very preterm infants.1 In clinical care, improved respiratory support strategies, antenatal steroids, surfactant therapy and other advances increased the survival of extremely preterm infants, after which they suffered from high risk of BPD. Therefore, the incidence of BPD did not decrease over the past decade.1 Nowadays, BPD often occurs in infants born at 24–28 weeks post menstrual age (PMA), with body weight (BW) [?] 1000g.2, 3 Premature infants have underdeveloped lungs and the severity of BPD increases due to the earlier gestational age (GA) and lower BW. BPD infants suffer from prolonged oxygen inhaling, higher incidence of respiratory infections and morbidity, as well as other forms of chronic lung illness and neurological impairment till the adult time.1, 4-6

As more extremely preterm infants survived all these years, the definition of BPD was revised. How to define BPD and predict clinical outcomes are still big challenges. Extremely preterm infants who lack a BPD diagnosis at 36 weeks PAM are still at increased risk of abnormal pulmonary function late in childhood and adulthood.7 In the latest NHLBI 2018 revision, based on the level of respiratory support, the severity of BPD is graded at 36 weeks PMA mainly that was proved to be useful to predict death or serious respiratory morbidity.8,9 However, BPD presents heterogenous phenotypes and the definition does not provide insights into the underlying cardiopulmonary and large airway impairment. For preterm infants, early injury of the developing lung impairs angiogenesis and alveolarization, resulting in the simplification of the distal lung airspace and significant pulmonary vascular disease. PH is common in BPD patients and has a major impact on survival rate. Pulmonary vasodilator medications were adapted worldwide. Mechanical ventilation and endotracheal intubation may deform the immature airway, thus leading to large airway lesions (LAL), mainly including tracheomalacia or bronchomalacia.10 LAL may increase oxygen support duration and pulmonary infections. The cardiopulmonary and large airway pathologic processes are well described and there is growing interest in the potential association between these phenotypes and prognosis.11-13. Based on their predominant clinical phenotypes, the stratification of BPD infants into subgroups is likely to enable better risk stratification.11

Chest radiographs, high resolution computed tomography (HRCT) and magnetic resonance imaging (MRI) were used to assess the degree of BPD-associated lung damage.14-16. Among these, HRCT is considered as the most accurate and sensitive imaging modality for the detection of pulmonary structural abnormalities and may be a predictor for later outcomes.16 However, the relations between HRCT and BPD clinical phenotypes and prognosis are still not clear. In order to identify those infants who are at greatest risks of poor outcomes, there is an urgent need to figure out the most sensitive feathers of HRCT to develop better strategies

of monitoring and treatment. Therefore, the aim of this study was to explore the associations of HRCT abnormalities with BPD phenotypes and clinical outcomes in preterm BPD infants.**MethodsSubjects' clinical data** This was a retrospective, single-center study of preterm infants suffering from BPD. The enrolled BPD infants were admitted to Children's Hospital of Fudan University between 2013 and 2020 and the clinical information was reviewed via medical records system. Clinical information included GA, BW, the duration of total respiratory treatment, the existence of PH and LAL, and the clinical outcomes (death before hospital discharge, home oxygen therapy and home pulmonary vasodilator therapy). Other parameters could affect the development of BPD, such as Apgar score of 1 and 5 minute, and the use of surfactant, antennal steroids, histological chorioamnionitis and patent ductus arteriosus were also compared. PH was diagnosed with echocardiogram by using systolic pulmonary artery pressure [?] 30mmHg and tricuspid regurgitant jet velocity. LAL was defined as tracheomalacia or bronchomalacia on bronchoscopy or HRCT. BPD was evaluated by chest X-ray as routine exam and HRCT was a standard practice for BPD preterm infant [?] 32 weeks. We excluded infants with congenital pulmonary deformity, serious pulmonary infection, severe congenital cardiac disease, and death before diagnosis of BPD. According to the NHLBI 2018 revision, the definition and severity grading of BPD were identified.8 Based on the need for oxygen support after 28 days or at 36 weeks PMA, all the subjects were graded as mild, moderate, and severe BPD. The study was approved by the institutional review board and parental consents were achieved from every patient. We assessed the association between HRCT scores and the phenotypes, and individual and composite outcomes (death before discharge, systemic pulmonary vasodilator after discharge and home oxygen therapy). The non-mortality outcomes were chosen, because they are strongly associated with adverse childhood outcomes and financial cost in families.11,17

HRCT protocol

Chest HRCT was performed between 36 weeks PMA and discharge (40-50 weeks PMA). This time range ensured a consistent time point of HRCT evaluation in this cohort. HRCT was conducted using 64-detector scanner (GE Healthcare, Princeton, NJ) with a tube voltage of 80 kVp, and a tube current of 60 mAs. The images were acquired at end-inspiration from the apex of chest to the diaphragm. All CT scans had a reconstruction slice thickness of 0.625 mm. Infants were either sedated with oral chloral hydrate (25 mg/kg) or asleep after feeding.

HRCT scoring protocol

For HRCT scoring, we adopted a HRCT scoring system for BPD that has been mostly used in the recent 10 years and made some modification.14,18-20. We evaluated six pulmonary lobes (left upper lobe, left lingual segment, left lower lobe, right upper lobe, right middle lobe, and right lower lobe) and examined seven types of lesions in each lobe to identify the presence of pulmonary abnormalities. Seven types of pulmonary lesions were categorized into two types: hyperaeration and parenchymal lesions. Hyperaeration lesions include decreased attenuation, mosaic attenuation, bulla/bleb, while parenchymal lesions involve linear lesion, consolidation, bronchial wall thickening, and bronchiectasis. The radiographic definitions were defined by the Fleischner Society nomenclature.21 Decreased attenuation was defined as an area of reduced lung attenuation and mosaic attenuation was a nonhomogeneous lesion that exhibited various attenuations. Bulla ([?] 1 cm) or bleb ([?] 1 cm) referred to round local lesions with reduced attenuation. Consolidation represented a homogeneous increase in parenchymal attenuation with blurred blood vessel and bronchial wall boundaries, linear lesion marked a thin and extended lesion along with soft tissue attenuation, and bronchiectasis stood for a widened airway compared to the accompanying pulmonary blood vessels. For each lobe, 1 point was given for the presence of an abnormal lesion of the seven parameters, and 0 points were given if the lesions were not present. The maximum score for each lobe was 7 points. The total HRCT score of 6 lobes wad summed, including the hyperaeration score (HS), the parenchymal score (PS) and the total score (TS). Hence, a higher score reflected more severe pulmonary disease. HRCT images were analyzed independently by two radiologists without information of any clinical data. TS, HS and PS were compared

for inter-observer agreement evaluation. The scans were reviewed by 1 observer 1 month later to measure intra-observer agreement.

Data analysis

Statistical analyses were carried out with SPSS (version 26.0, IBM, Armonk, NY). Continuous parameters are expressed as the mean ± standard deviation or minimum-maximum range. Categorical parameters are expressed as numbers or percentages, as appropriate. The correlation between HRCT scores and clinical phenotypes and outcomes were evaluated by Spearman's correlation analysis. For comparisons of HRCT scores among different clinical phenotypes, one-way *ANOVA* testing and unpaired student$t$ test were adopted. The association between the evaluated BPD phenotypes and outcomes and HRCT scores was assessed applying logistic regression. Odds ratio (OR) and 95% confidence interval (CI) were calculated. The intra- and inter-observer agreement of HRCT scores were evaluated with Cronbach's α coefficient. When p values were <0.05, statistical significance was achieved.**ResultsClinical characteristics of infants' study**All the clinical data was listed in Table 1. We identified 107 infants with BPD diagnosed at 36 weeks PMA and experienced chest HRCT through medical system. Among them, 5 neonates were excluded due to the poor quality of images, 10 developed with severe pulmonary infection and congenital heart disease, and 11 neonates were excluded because the HRCT was performed much later after discharge. Finally, 81 infants (56 male and 25 female; GA, 28.93 ± 2.25 weeks; BW, 1335.86 ± 456.80 g) were enrolled in this study.

HRCT scores with the severity of BPD

A total of 17 (20.99%) infants were classified as mild BPD, 31 (38.27%) as moderate BPD, and 33 (40.74%) as severe BPD. In Table 2, more severe BPD presented lower GA and BW, and longer duration of oxygen support, while there was no significant difference among the 3 groups. Higher TS (p=0.01), HS (p=0.02), and PS (p=0.02) were discovered in more severe BPD group with significant difference. Mosaic attenuation (p=0.03), bulla/Bleb (p=0.03) and linear densities (p=0.01) also demonstrated difference in more severe BPD group with significant difference. By Spearman's correlation analysis, TS (r=0.49, p=0.00), HS (r=0.31, p=0.00), and PS (r=0.30, p=0.01) were correlated with the clinical severity of BPD. Decreased attenuation (r=0.21, p=0.04), mosaic attenuation (r=0.31, p=0.01), bulla/Bleb (r=0.27, p=0.02) and linear densities (r=0.55, p=0.00) also demonstrated a correlation with BPD severity.**HRCT scores with HP and LAL** All the data was listed in Table 2. Totally, 40 (49.38%) infants had PH, 8 in mild BPD, 13 in moderate BPD, and 19 in severe BPD. PH (+) group indicated lower GA and BW, and longer duration of oxygen support, and GA (p=0.02) had significant difference. TS (r=0.28, p=0.01), PS (r=0.35, p=0.00), linear densities (r=0.34, p=0.00) and consolidation (r=0.24, p=0.03) were higher in PH (+) group and displayed a correlation with PH. A total of 20 (24.69%) patients had LAL, 3 with mild BPD, 7 with moderate BPD, and 10 with severe BPD. GA, BW and the duration of oxygen support did not show significant difference between LAL (+) and LAL (-) groups. All the HRCT scores did not show difference between the 2 groups.

HRCT scores among different combination of phenotypes

All the patients were subdivided into 4 groups: BPD (Group 1 = 39), BPD+HP (Group 2 = 22), BPD+ LAL (Group 3 = 9), and HP+LAL+BPD (Group 4 = 11). Compared with G1 and G3, G2 and G4 experienced more severe pulmonary impairment. G4 had the highest TS and HS, and G2 got the highest PS. All the values did not have significant difference (Figure 1). Other clinical variables, including antenatal steroid administration, chorioamnionitis and PDA were compared among the 4 groups and no significant difference was identified.**HRCT scores predicting outcome**When the HRCT scores were treated as a continuous variable, TS (OR 1.11, 95% CI 1.01-1.21, p=0.03), PS (OR 1.17, 95% CI 1.01-1.36, p=0.03) and linear densities (OR 2.23, 95% CI 1.34-3.71, p=0.01) was related to the composite outcomes with significant difference. When individual components of the primary outcomes were separately assessed, linear densities (OR 2.30, 95% CI 0.96-5.49, p=0.01), TS (OR 1.16, 95% CI 1.01-1.33, p=0.03) and HS (OR 1.17, 95% CI

1.01-1.35, p=0.03) was associated with pulmonary vasodilator. Consolidation (OR 2.09, 95% CI 1.07-4.08, p=0.01) and PS (OR 1.27, 95% CI 1.00-1.60, p=0.02) was closely related to the increased risk for the death. Linear densities (OR 2.36, 95% CI 1.22-4.57, p=0.01) were risk factors of home oxygen therapy. All the data was listed in Figure 2.**Intra- and Inter-observer agreement** We evaluated the intra-observer and inter-observer agreement with Cronbach's α coefficient. If the value is higher than 0.8, the reliability is high. If the value is between 0.7 and 0.8, the reliability is good. If the value is between 0.6 and 0.7, the reliability is acceptable. If the value is less than 0.6, the reliability is poor. In this research, inter-observer agreement was high for HS (Cronbach's $\alpha = 0.85$), PS (Cronbach's $\alpha = 0.90$), and TS (Cronbach's $\alpha = 0.88$). Inter-observer agreement was high for HS (Cronbach's $\alpha = 0.82$), PS (Cronbach's $\alpha = 0.86$), and TS (Cronbach's $\alpha = 0.86$).

Discussion

Over the last few decades, the incidence of BPD did not decrease and remained as the most common late morbidity of preterm birth. Low BW and low GA were associated with the higher incidence and higher severity of BPD. In China, the overall incidence of BPD was about 1.28% in 2011, with 19.3% among extremely preterm infants (<28 weeks).22 In 2001, the NIH consensus proposed the first widely accepted definition of BPD, namely a requirement for supplemental oxygen for at least 28 days. According to the oxygen treatment at 36 weeks PMA, BPD was classified as mild, moderate, or severe.23 The definition has been fixed in all these years.24 Meanwhile, with the higher survival of extremely low BW and GA premature infants, "new" BPD that is caused by immature lung development has become the dominant type of BPD.17 In new BPD, alveolar simplification and dysmorphic pulmonary vascularization are two main histopathological features, while for "classic" BPD, extensive inflammatory and fibrotic changes are the characteristics.25,26 Although the current criteria improved the stratification of BPD severity, using respiratory support alone did not adequately inform the underlying pathophysiology. BPD is a heterogenous lesion that affect three main lung compartments, including airways, lung parenchyma, and the pulmonary vasculature. A better understanding of BPD phenotypes is useful for better risk stratification for patients. The disruption of distal lung growth with impaired alveolarization can lead to hypercarbia, hypoxemia, and oxygen support. Abnormal growth of the pulmonary microvasculature can result in pulmonary vascular disease, and most commonly manifests as PH that impacts 16–25% of BPD infants 11, 27 and has a major impact on the higher mortality risk for very preterm infants.3,17,25,28 Khemani proved a progressive decline in survival during a longitudinal study of infants with BPD and PH, in which only 52% of infants survived after 3 years.29 A majority of PH patients need regular screening and specific pulmonary vasodilator therapy. Clinical manifestations of LAL in BPD presents are mainly bronchomalacia or tracheomalacia, and localized or generalized.30,31 The frequency of tracheomalacia among BPD patients varies from 10% to 46%.32 The extensive airway collapse can cause ineffective cough and clearance of secretions, leading to increased risk of respiratory infections, prolonged recovery, and recurrent or persistent pneumonia 33. The complex pathophysiology of BPD can cause phenotype variability, which was reported to be associated with clinical outcome.11,34 In this cohort, almost half of patients were diagnosed with at least two or more disease components. The combination of BPD and PH was the most common type. The combination of phenotypes exhibited important associations with pulmonary impairment, especially for the patients with PH who need special monitoring and long-term follow up. We focused on understanding the potential interaction of pulmonary impairment and predominant clinical components and outcomes of BPD. Most researches categorized pulmonary abnormalities into two types of lesions: hyperaeration lesions and parenchyma lesions and many studies demonstrated a correlation between HRCT score and BPD severity. 14,19,35 In our study, TS, PS and HS all displayed association with the severity of BPD, which supported that the grading of the severity of BPD is useful to predict serious respiratory impairment. For "new" BPD, "arrest" in alveolation is a hallmark on HRCT which was also found in our research. Decreased attenuation, mosaic attenuation and bulla/Bleb all demonstrated a correlation with BPD severity. The hyperaeration lesions were the most common feather in BPD, and revealed the most sensitive structural abnormality associated with BPD severity.18,36 This imaging feature was maybe due to the alveoli expanding, partial airway obstruction, and hypo perfusion from the impaired pulmonary vasculature.

The severity of hyperaeration was also reported to be correlated with other obstructive lung diseases.37,38 For cystic fibrosis, the quantification of the volume fraction of low attenuation regions is a promising predictor for future impaired lung function. Almost half of our patients had PH, most in severe BPD group. In terms of PH risk factor evaluation, TS and linear densities displayed a correlation and presented as risk factor for pulmonary vasodilator. On HRCT, linear opacities are frequent in BPD, maybe the most common findings on CT and they probably reflect alveolar septal fibrosis, thus leading to obstructive ventilation impairment and PH.36,39,40 In longitudinal studies, these opacities did not change over time and may be considered as irreversible damage in late BPD.37 This CT features also illustrated a correlation with BPD severity. Consolidation was another dominant feature in BPD patients. In our research, consolidation was related with PH and was risk factor of death. Perhaps, large areas of consolidation were related with severe infection, hypercarbia, hypoxemia and respiratory failure. Other structural changes such as bronchiectasis and bronchial wall thickening were often reported in other interstitial lung diseases including cystic fibrosis, and were less frequent in BPD at early stage. At the same time, we found that LAL was not related to the HRCT imaging features. Maybe the cause of LAL was long-term intubation and barotrauma, different from cardiorespiratory developmental impairment. In our medical center, chest radiography was applied in daily clinical practice for BPD. However compared with HRCT, it cannot give enough detailed information to properly reflect the abnormalities in the pulmonary parenchyma and to predict the clinical severity of BPD.18 HRCT can provide more objective and detailed information about pulmonary structural damages with BPD and has the potential to predict later symptoms and impairments. Considerable CT scoring methods were adopted over the last 30 years to semi-quantify the structural abnormalities in BPD.16,35. All studies proved abnormal CT findings in patients with BPD. However, none was validated to be superior over another and there was no universally accepted CT scoring system yet.35 In our study, we adapted the HRCT scoring system that was modified from the widely used model in the recent 10 years in four papers and made some modification.14,18-20 This scoring system included the most distinguishing features for BPD and is likely to influence the respiratory prognosis to some extent. We believe that this scoring system can reflect all the aspects of BPD pulmonary impairments and evaluate the imaging features from an objective and reproducible perspective. This HRCT scoring system also presented good inter-observer and intra-observer reproducibility.18,36 Multiple perinatal factors are known to significant in BPD development. GA, BW, and duration of oxygen treatment have been the most described items. Barotrauma and volutrauma are caused by mechanical ventilation and the use of high concentrate of oxygen in preterm infants is believed to be the main mechanisms underlying BPD. Most studies revealed a significant correlation between the duration of oxygen treatment and CT scores.19,20,41 At the same time, low GA and BW are well-known causes of the development of BPD. An extremely preterm birth can significantly impair alveolarization and normal lung growth, even within normal room air.8 In this study, we concluded that lower GA, lower BW, and longer duration of oxygen support were correlation with BPD severity and the risk of PH. The present study has certain limitations. First, we did not include all the mild BPD patients for the lack of HRCT. Second, the standardized HRCT scoring system was insufficient in a large population. Third, in order to simplify the scoring system, the score within each BPD segment was not taken into account in the research. We should modify these points in the future work.**Conclusion**In conclusion, this study revealed that HRCT scores were correlated with the BPD severity, PH, and poor clinical outcome. The hyperaeration lesions were more related with BPD severity. Linear densities related with PH and consolidation was risk factor of death. Our study indicated that HRCT can help improve BPD phenotyping with better objective measurements of lung impairments.

Ethics approval and consent to participate Informed consent forms were signed by the parents and ethics approval was approved by the institutional review boards of the Children's Hospital of Fudan University.**Competing interests**The authors declare that they have no competing interests**FundingThe National Key Research and Development Program of China (2016YFC1000500)Authors' contri-**

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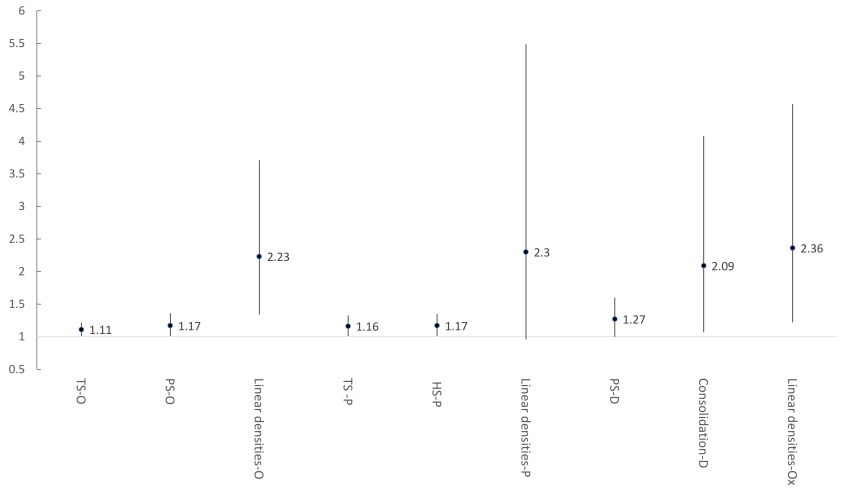

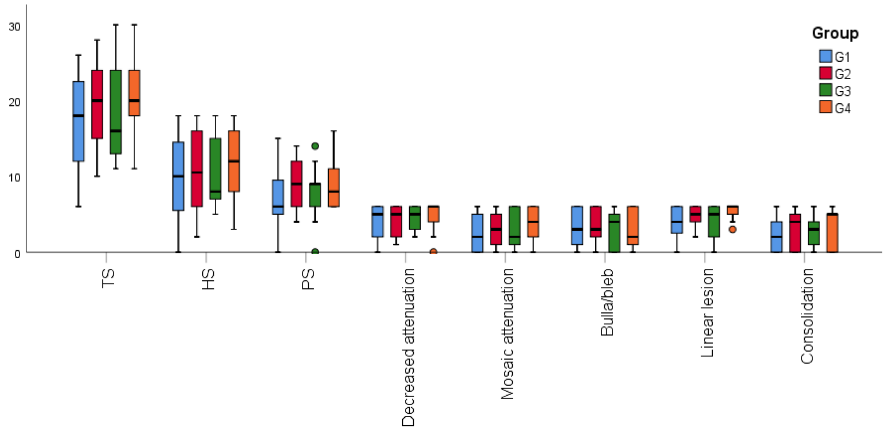

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