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Assessing Lung Vasculature Development and Application to Early Pre-term Gestation Patients: A Second Look

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Abstract

Bronchopulmonary Dysplasia (BPD) is a chronic respiratory disease associated with preterm gestation. It presents itself in patients from birth through reliance on ventilation devices due to improper lung development. Although the lungs become more independent through infancy, they never develop fully, leading to complications through adolescence and adulthood. This study continues the work done in 2022 by Dias and others, which sought to map the lung vasculature of preterm gestation patients and compare it to full-term gestation patients over time to track the development of lung vasculature. This was achieved using modified ImageJ software to create a 3-D model of the right lung vasculature. Lung vessels were counted from these 3-D models and compared to evaluate whether a correlation exists between lung vessel counts and gestation age. So far, no definitive evidence has been shown for a correlation.

Keywords: lung vessel development, x-ray Computed Tomography, pediatric

Background

In recent years, advancements in medical knowledge and technology have allowed for greater chances of survival for infants born prematurely. However, this is not without its complications, as premature infants have less time to develop in the womb. Pre-term birth poses serious health risks that may be both acute and chronic due to improper organ development. Chronic lung disease, also named bronchopulmonary dysplasia (BPD), is a chronic health burden for pre-term infants arising from improper development of the lungs (Carregã et al., 2023). Specifically, BPD affects the alveolarization of the lungs, meaning less surface area to allow for gas exchange from the capillaries (Moschino et al., 2021). Thus, pre-term infants are put on ventilation devices that provide the necessary oxygen for survival. External factors may contribute to BPD development, including invasive ventilation, inflammation of the lungs, and the use of surfactants (Xu et al., 2023; Bauer et al., 2020). Since BPD is chronic, it continues into adulthood with clinical manifestations resembling obstructive pulmonary diseases (Moschino et al., 2021; Cassady et al., 2020)

BPD can be detected using various radiographic techniques (Moschino et al.,2021; Alonso-Ojembarrena et al., 2023). Alonso-Ojembarrena et al. wrote a review that covered the different methodologies for detecting BPD, including chest radiography (CXR), computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI). Specifically for CT scans, lung aeration was measured by comparing pixel intensities of air in the lungs with surrounding tissue (2023). The present study also utilized CT scans but were instead used to map out the 3-dimensional space of the lungs, allowing insight into key internal characteristics such as vasculature.

Possible later alveolarization of the lung may also lead to varying symptoms of adult BPD (Carregã et al., 2023). Manifestations of adulthood BPD include asthma-like symptoms of wheezing and respiratory tiredness, as well as emphysema, obstructive lung disease, and pulmonary hypertension (Carregã et al., 2023; Moschino et al.,2021; Cassady et al., 2020). Emphysema and obstructive lung disease-like symptoms of BPD usually arise in older patients whose premature birth was before the invention of external surfactants. Less severe versions of BPD emerged due to the greater widespread use of artificial surfactants in infancy, which are usually associated with asthma-like symptoms in adulthood (Cassady et al., 2020).

Since BPD is a life-long disease, the present study wanted to observe lung vasculature development along multiple CT scans across pediatric patients' maturation to track the rate of lung vasculature development. The purpose of this study was to continue the work of Dias and others in investigating any possible correlations between gestation age and lung vasculature characteristics over multiple CT scans throughout the patients' lives.

To determine if such correlations exist, two hypotheses were proposed. First, the data gathered must have a significant trend of vascular maturation with time for both pre-term and full-term patients. Lung vessel maturation trends will be considered significant if fitted to a regression line or curve with an R-squared value of 0.70 or greater. If both groups are fitted to trendlines with an R-squared value of 0.70 or greater, the second hypothesis follows, which examines if there is a significant difference in the slopes of the trendlines between the two groups. If both the first and/or second hypotheses are not met, then the null hypothesis would be assumed, implying no significant correlation between gestation age and lung vasculature over time with the presented evidence.

Methodology

Under IRB approval (protocol: IRB201900733 *Retrospective analysis of chest CT scans in pediatric patients to monitor development of lung vasculature, particularly for those born prematurely*), the study has access to 60 pediatric patients, each with at least 3 chest scans taken at varying ages under 18 years old. 30 of these patients were born prematurely at 36 weeks or less gestation age. The other 30 patients have a gestation age of 37 weeks or more and have been cross-matched by age to the pre-term patients for comparison. These patients performed chest CT scans at one pediatric academic center between 1/1/2010 and 3/2/2019. To avoid selection bias, patients were chosen without knowledge of sex, gestation age, or past relevant medical history. Additionally, sex, gestation age, and past relevant medical history were only revealed to the research team after image analysis to prevent confirmation bias. CT scan slice thickness ranged between 1 and 3 mm, with a few CT scans having a 5 mm slice thickness. Additionally, pixel spacing (in-plane pixel dimensions) ranged from 0.332 to 0.812 mm.

ImageJ, an NIH-built imaging software, was used as the foundational program to analyze the CT scans for each patient (Schneider, 2012). Analysis functionalities were coded into the program to map out the lung vessel structure from the CT scans. Primarily, vessel segmentation software was used to map out the lungs and extract their major airways and vessels. Only the right lung was used for CT scan analysis due to its larger size, as well as some patients having diseased left lungs. The CT scan images were inputted into the ImageJ vessel segmentation program to analyze the lung CT scans. Then, a series of thresholding and processing steps followed that defined the outer lung border, which may be manually adjusted using the *snake* program (O'Dell, 2012). Lung thresholding was usually set to filter lung volume at either -440 or -560 Hounsfield units, depending on the clarity of the CT scan. After defining the lung border, the major airways are segmented and removed using a seeded-region-growing method for low-intensity voxels to ensure airways are not counted as part of the vasculature. Then, pulmonary vessels are segmented using the same seeded-region-growing method, but high-intensity voxels are sought where the seed is placed at the pulmonary trunk. The pulmonary vessel tree structure is then skeletonized to allow for traversal and labeling of the branches (O'Dell, 2014). Finally, the program counts the number of pulmonary vessel branches and measures the radius and length of each branch (O'Dell, 2017).

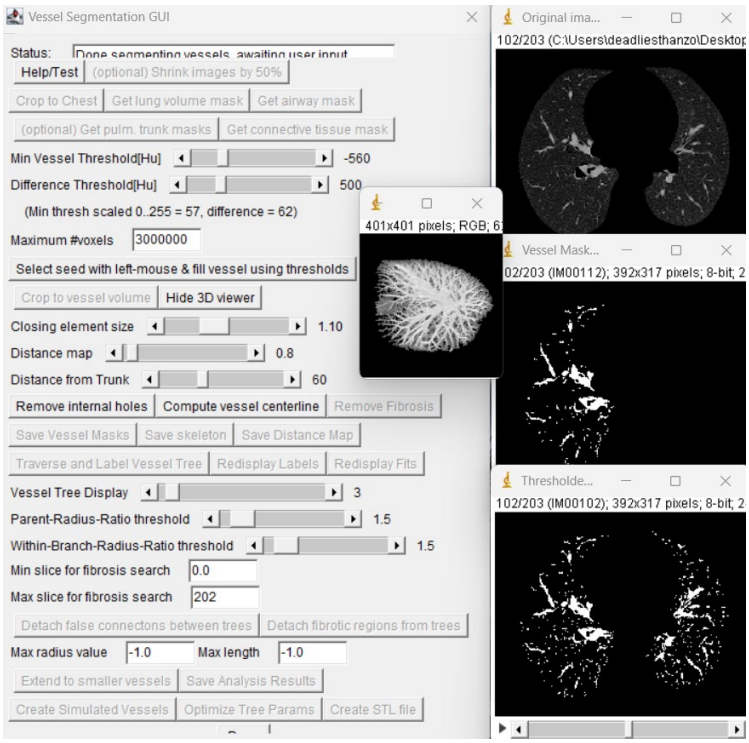

Figure 1: The CT scan input of the lungs is segmented and converted to show areas of high (white) and low (black) voxel intensity. After the right lung is chosen, the software creates a 3D model of the lung vasculature that's used for numerical analysis and comparison.

The data gathered from the lung segmentation program was recorded in a spreadsheet, alongside information about gestational age, sex, and relevant medical history. Data analysis followed after a designated number of patients had been analyzed, using scatter plots as a comparison tool. Calibration curves were also used to adjust for variability in imaging parameters (Martocci, 2021). Only vessels with a radius greater than 1 mm were used to increase accuracy and precision.

Dias and others (2022) were able to analyze the first 21 patients out of the 60-patient cohort. Data was collected on 16 patients; the other 5 were voided due to unclear scans affecting analysis. This study serves as a continuation of her work with the analysis of 9 more patients. Therefore, half of the 60-patient cohort has been analyzed to find a correlation between lung vessel counts and gestation age.

Results

Out of the 16 patients initially studied, nine were full-term, while seven were pre-term, with an equal distribution of males and females. This study adds nine more patients, six of which were

pre-term patients and three were full-term. Of the pre-term patients, four were female, one was male, and one was unspecified. Of the full-term patients, two were female, and one was male. Each subject provided at least three scans, with one patient providing 18 scans. Scans were taken as early as nine months, fourteen days gestational age to as late as 18 years, six months, seven days gestational age.

Figure 2 shows some of the data gathered for the 25 patients analyzed. An exponential regression line gave the best R-squared values but remained insignificant. This leads to an assumption that lung vessel branches increase exponentially with age. Razavi et al. used a novel way of quantifying lung vessel development using rat models, finding exponentially greater lung vessel counts with greater age until a certain point of stability (2012). Additionally, lung vessels had larger diameters (and therefore larger radii) with increasing age. Since the scope of the research was limited to lung vessels with a radius of 1 mm or greater, a greater number of vessels could then be analyzed with increasing age, which could typify exponential growth, especially in childhood.

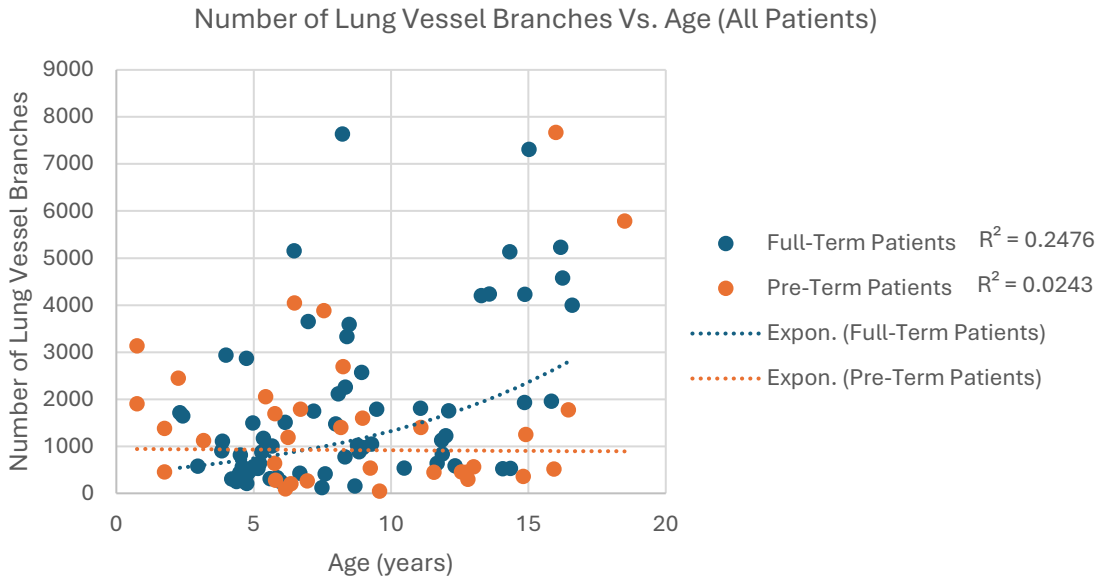

Figure 2: Scatter plot showing number of lung vessel branches on the y-axis and age in years on the x-axis. Full-term patient data is shown with blue dots while pre-term patient data is shown with orange dots. The plot uses data from all patients analyzed (both the present study and Dias et al.'s study). Exponential regression lines are fitted with R squared values shown.

Even with exponential regression lines, there is a considerable amount of variability in the data. More variance was observed in the pre-term patients compared to the full-term patients regarding the progression of lung vessel branch counts with age. Full-term R-squared values, however, remained small. A possible hypothesis is that the full-term patients analyzed had comorbidities that made consistency difficult in the vessel segmentation program. Since the exponential regression lines had small R-squared values for both groups, no major differences were observed in lung vasculature between pre-term and full-term patients.

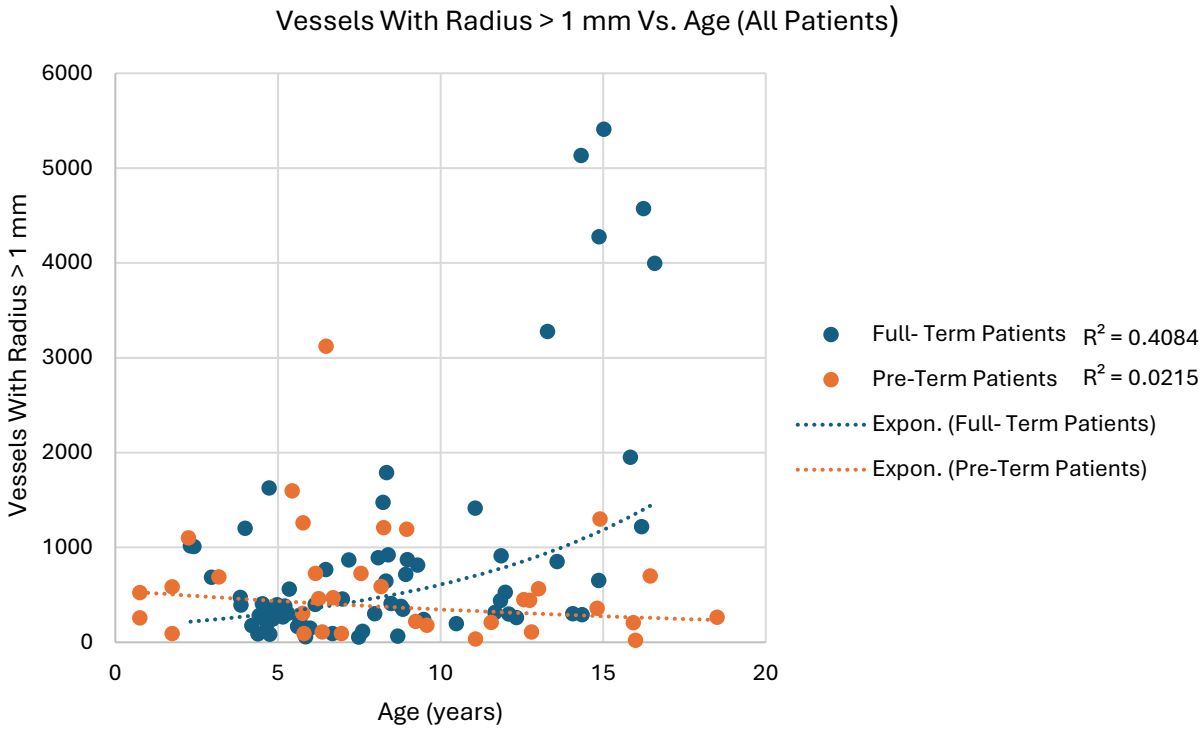

Figure 3: Scatter plot showing number of vessels with a radius greater than 1 mm on the y-axis and age in years on the x-axis. Full-term patient data is shown with blue dots and pre-term patient data is shown with orange dots. The plot uses data from all patients analyzed. Exponential regression lines are fitted with R squared values shown.

The study's most significant finding comes from Figure 3, showing the progression of the number of vessels with radius exceeding 1 mm with age in years. When fitted to an exponential regression line, full-term patients show an increasing trend with an R-squared value of 0.40. Pre-term patients have an R-squared value of 0.02, showing considerable variability in the data. Although the R-squared values are low, one may hypothesize that full-term patients have more consistent vasculature development than pre-term patients. Additionally, this variability may also

be due to the varying weights and sexes of the patients that may contribute to lung vasculature development.

Discussion

The combination of the present study and Dias and others' study have analyzed 30 patients out of the 60-patient cohort. Out of those 30 patients, five presented pulmonary comorbidities in their CT scans that prevented further analysis. Therefore, 25 patients were thoroughly analyzed using vessel segmentation software. Both studies aimed to find a correlation between lung vasculature development and pre-term birth. However, no significant trends of lung vasculature were observed for both groups, using the R-squared value of 0.70 and above as a metric of acceptable trends. Therefore, the study could not accurately compare the lung vasculature between the pre-term and full-term groups. Premature birth may still produce underdevelopment of lung vasculature, but its presentation may be more complex, especially in the context of BPD and its other clinical manifestations.

Future research may work to improve on the difficulties the present study faced. The vessel segmentation software encountered some problems, which were continually being addressed throughout the study with some success. Although the segmentation software should work efficiently on grown healthy adults, pediatric patients with complex pulmonary morbidities present an obstacle to the program. This is the case with both full-term and pre-term patients, as receiving a CT scan, especially with pediatric patients, would not be customary without a hypothesis of a pulmonary disease. An example is lung pneumonia, seen in Figure 4, an issue encountered in multiple patients' CT scans. Since pneumonia is registered as a high-intensity region in the lung airspace, detecting lung vasculature underneath it is difficult. The study is investigating a workaround to this problem by predicting the lung vasculature blocked by pneumonia and traversing the predicted branches. However, this has not fully been implemented.

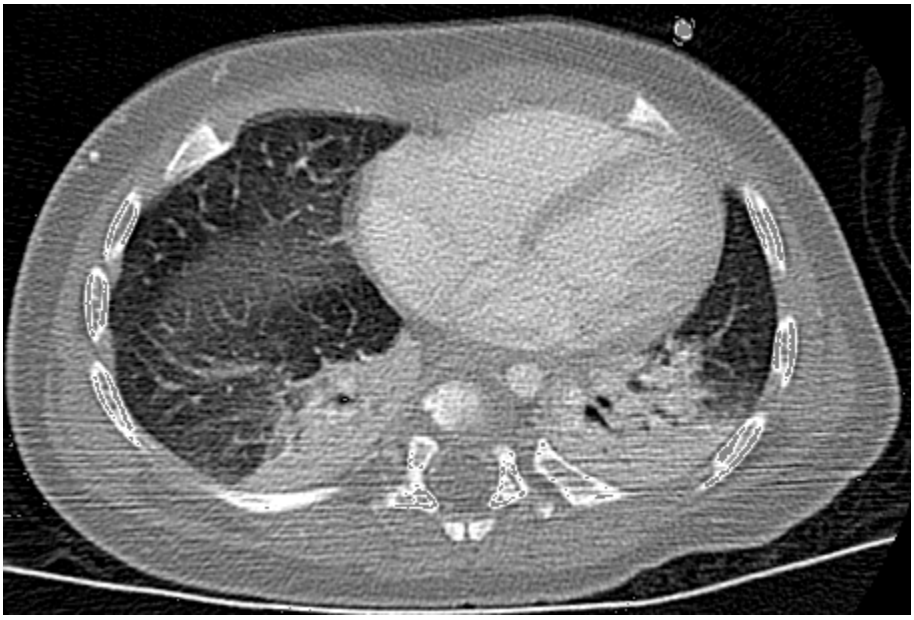

Figure 4: CT scan of a pre-term patient at gestation age 1 year, 2 months, 5 days. The CT scan contains white blobs at the posterior of both the right and left lung which block the lung vasculature. Additionally, the CT scan's low resolution makes it even more difficult to segment.

Additionally, CT scans of younger pediatric patients may lead to images with suboptimal resolution. Figure 4 shows how blurry CT scans may become with younger children, such as the patient shown, whose gestation age was just over a year. CT scans require the patient to be still and hold their breath so that the CT scan images may be taken, presenting an obstacle to infants and toddlers who tend to be restless and may not have the knowledge to hold their breath safely. With this constraint, CT scan resolution is sacrificed, leading to blurry and hard-to-traverse 3D models of lung vasculature.

Although some identified issues resulted from the study's nature, other internal difficulties remained, primarily with the code. Even with continual optimization, the program had many glitches that may have produced inconsistencies in the results. This can be seen in Figure 5, which presents the lung vessel counts for a full-term patient as they became older. This patient's data should be the most accurate measure of healthy lung vasculature, yet it is inconsistent and confusing to interpret. Therefore, greater code optimization is necessary to achieve more accurate and precise results of lung vasculature.

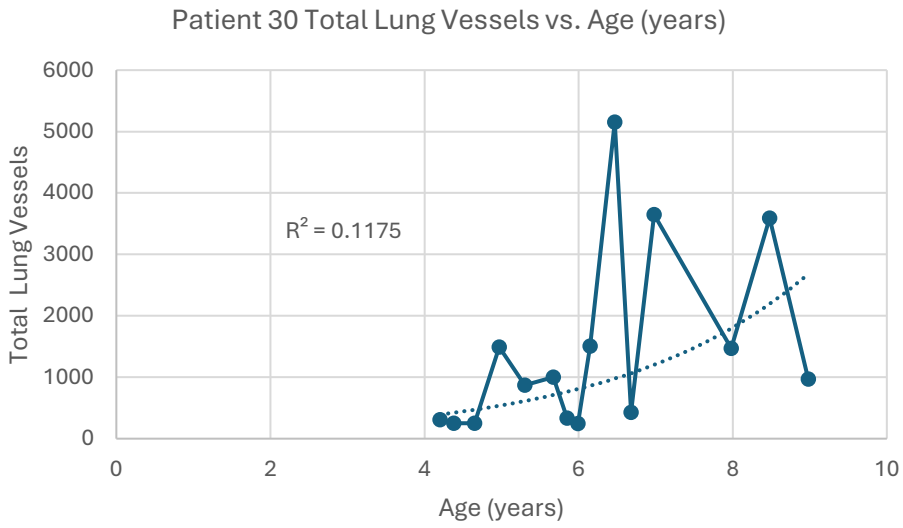

Figure 5: Scatter plot showing the progression of the total number of lung vessels of one full-term patient with age in years. An exponential regression line was fit to the data with the R squared value shown.

Conclusion

The study did not have significant findings to prove the first hypothesis, as the highest R-squared value achieved for all the data was 0.40, which is below the 0.70 threshold previously set. Therefore, the study fails to reject the null hypothesis due to the lack of a significant trendline for vascular maturation for both groups. Therefore, the study could not further investigate the second hypothesis that examines the difference in the slopes of the trendlines and lacks strong evidence to show a considerable difference in lung vessel maturation between pre-term and full-term pediatric patients. Although the study did not find any significant data, its approach may be important for the benefit of pre-term patients. Understanding the progression of lung vasculature, especially in pre-term patients, allows for a better understanding of the underlying mechanisms behind improper lung development. With greater insight, medical intervention may be specified to target the disease and improve patient well-being.

Additionally, the improvement of CT scan technology and software may create an environment where the implementation of this research method is possible. Literature is increasingly using CT scans for 3D modeling of visceral organs, and introducing artificial intelligence may boost the accuracy and precision of these methods. Therefore, future research

using more modern imaging techniques may allow for a breakthrough that may improve overall human health.

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