THE ADDED VALUE OF CARDIAC MAGNETIC RESONANCE IMAGING THRESHOLDS FOR ASSESSMENT OF PULMONARY HYPERTENSION IN PEDIATRIC INTERSTITIAL LUNG DISEASE

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Abstract

Background: Interstitial lung disease comprises a heterogeneous group of disorders in which there is a predominantly restrictive pattern of lung disease. It is characterized by derangement of alveolar walls and the loss of alveolar-capillary units and variable degree of fibrosis which results in destruction of pulmonary vascular bed, oxygen diffusion impairment and hypoxic pulmonary vasoconstriction that will lead to pulmonary hypertension.

Aim: To identify the added value of Cardiac Magnetic Resonance Imaging thresholds for assessment of pulmonary hypertension and right ventricular function in Pediatric interstitial lung disease complicated by pulmonary hypertension.

Methods: A total number of 34 cases, both males and females, less than 18 years old known to have interstitial lung disease proved clinically and radiologically complicated by pulmonary hypertension were included in this study. By using 1.5 T CMR scanner equipped with 32 channel cardiac coils, we performed steady-state free precession cine CMR to assess the right ventricular function. Other risk stratification tools of pulmonary hypertension (echocardiography-Pro BNP- 6 MWT- speckle tracking Doppler) were also done. The study group assessed initially and follow up done after a period of 6 months of treatment.

Results: The study group consisted of 34 cases; 13 males (38.2 %) and 21 females (61.8%). The mean age was 8.22 ± 4.22 years old. The mean estimated systolic pulmonary artery pressure (ESPAP) pressure was 67.80 ± 27.40mmHg detected by echocardiography. The mean right ventricular ejection fraction (RVEF) detected by cardiac MRI was 50.33 ± 9.30%. By comparing the initial and the follow up group, there was statistically significant difference regarding ESPAP (p=0.044), EDPAP (p=0.017), RVEDV by CMR (p=0.022) and RVESV by CMR (p=0.030).

There was negative correlation between RVEF by CMR and systolic pulmonary artery pressure (ESPAP) (r=-0.522 & p=0.002) and GLS in the speckle Doppler (r=-0.412 & p=0.019).

Univariate linear regression analysis for the initial parameters affecting RVEF by CMR revealed that it is affected by (O2 saturation, systolic and diastolic pulmonary pressures, right ventricular and atrial dilatation and global longitudinal strain in speckle tracking Doppler).

Conclusion: The current study demonstrated the added value of cardiac MRI in assessment of right ventricular function in childhood interstitial lung disease complicated by pulmonary hypertension. CMR derived right ventricular ejection fraction (RVEF) might be useful for the risk stratification and clinical management of ILD patients.

Keywords: Childhood interstitial lung disease, pulmonary hypertension, cardiac magnetic resonance imaging

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1. INTRODUCTION

Childhood ILD is not a single disease but a large and diverse group of disorders. Because most childhood ILD entities present in a similar way, childhood ILD syndrome has come to be defined in terms of clinical presentation (respiratory signs and symptoms; diffuse radiographic abnormalities, with or without hypoxemia, in the absence of other causes of diffuse lung disease, such as cystic fibrosis, aspiration, infection, and immunodeficiency **(Deutsch et al.,2007).**

Fibrotic remodeling is responsible for most of the morbidity and mortality associated with ILD. Remodeling of distal airspaces results in hypoxemia. Persistent hypoxemia causes pulmonary hypertension and vascular remodeling, leading to cor-pulmonale. The increased work of breathing associated with reduced compliance raises energy expenditure, which, combined with the effects of inflammatory mediators, can result in cachexia. Portions of the lung may be replaced by fibrotic septa between dilated airspaces, the so-called honeycomb changes of end-stage interstitial disease **(Thannickal et al., 2004).**

Pulmonary arterial hypertension is defined as a mean pulmonary arterial pressure greater than 25 mmHg at rest, with a normal pulmonary artery wedge pressure less than 15 mmHg and an increased pulmonary vascular resistance greater than 3 Wood units×M2 **(Hoeper et al, 2013).**

The most common respiratory causes of pulmonary hypertension in children are severe chronic lung diseases, such as CF; ILD; and disorders of the respiratory pump, such as myopathies or severe spinal deformities. In infancy, chronic lung disease of prematurity or broncho pulmonary dysplasia is a more common cause of secondary pulmonary hypertension **(Roy and Couriel, 2006).**

Cardiac MRI is the recognized gold standard for assessment of right ventricular function and has a prognostic role in pulmonary arterial hypertension **(Benza et al., 2008).**

CMR provides comprehensive information about the anatomical and functional aspects of the pulmonary artery and right ventricle that are of prognostic significance for assessment of long-term outcomes in disease progression. CMR is suited for serial follow-up of patients with PH due to its non-invasive nature, high sensitivity to changes in anatomical and functional parameters, and high reproducibility **(Aryal et al., 2020).**

Hemodynamic and functional capacity parameters are currently the cornerstones in characterizing disease progression. Invasive obtainable hemodynamic parameters have been shown to represent disease severity and to predict survival. Non-invasive parameters for functional capacity are used for the assessment of clinical condition, severity of disease, and effectiveness of therapy **(Beghetti et al, 2013).**

2. PATIENTS AND METHODS

- **Study Population:**

A total number of 34 cases, both males and females, less than 18 years old known to have interstitial lung disease proved clinically and radiologically complicated by pulmonary hypertension were included in this study.

- This study was conducted at Faculty of Medicine, Cairo University Pediatric Hospitals.
- Study participants were recruited from pulmonology and cardiology clinic and Pediatric inpatient Pulmonology unit.

- **Inclusion criteria:**

- Age: 1 years to 18 years
- Gender: both gender included
- All patients diagnosed to have interstitial lung disease complicated by pulmonary hypertension were included in this study.

- **Exclusion criteria:**

- Other chronic lung diseases such as cystic fibrosis, bronchiectasis
- Other causes of pulmonary hypertension other than ILD such as congenital shunt lesions.

- **Methods**

Informed consent was obtained from caregivers.

All patients were evaluated clinico-radiologically for diagnosis of childhood interstitial lung disease and to detect pulmonary hypertension as a complication of ILD. They were subjected to full history taking, full clinical examination, laboratory investigations including; Pro brain natruiertic peptide (ProBNP), imaging studies including high resolution CT chest, echocardiography and cardiac magnetic resonance imaging.

- **Cardiac MRI Examination:**

Cardiac cine MRI was performed on a 1.5-T GE HDx MRI scanner using an eight channel receiver array and multi-slice balanced steady-state imaging with retrospective gating (20 frames per cardiac cycle; slice thickness, 8 mm; field of view, 48 cm; matrix, 256 3 256; bandwidth, 125 kHz/pixel; repetition time/echo time, 3.7/1.6 ms). A stack of images in the short axis plane with slice thickness of 8 mm (2-mm inter slice distance) was acquired covering both ventricles from base to apex. End systole was considered to be the smallest cavity area. End diastole was defined as the first cine phase of the R-wave–triggered acquisition or largest volume. Volumes were indexed for body surface area and then corrected for age and sex.

Global functional parameters were derived from cine MRI, with the aid of commercially available software. The endocardial borders of both ventricles were traced manually from the short axis images during systole and diastole. LV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated on the basis of Simpson‘s rule.

Subsequently, stroke volume (SV) and ejection fraction (EF) was calculated using EDV and ESV values.

The ventricular ejection fraction is classified into: Normal: 55-75%, Border line: 40-54% and low: <40%.

STATISTICAL METHODOLOGY:

Data was analyzed using IBM© SPSS© Statistics version 23 (*IBM© Corp., Armonk, NY*). Normally distributed numerical data presented as mean and SD and skewed data as median and interquartile range. Qualitative data presented as number and percentage.

Normally distributed numerical data were compared using the unpaired t-test. Skewed data was compared using the Mann-Whitney U-test. Categorical data was compared using the chi-squared test or Fisher's exact test, if appropriate. ROC curve analysis was used to examine the prognostic value of cardiac MRI measures and NT-Pro-BNP.

P-value < 0.05 was considered statistically significant.

3. RESULTS

A total 34 cases were reviewed with 13 males (38.2 %) and 21 females (61.8%). The median age was 9 years with IQR from (6-12). Anthropometric measurements in our study group were evaluated according to WHO standard deviation growth curves. The median weight was 20 kg with IQR from (15-28) and the median height was115 cm with IQR (105-131). The Median Body Mass Index was 15.63 with IQR (13.89 – 17.10) kg/m^2.

Table (1): Distribution of the studied cases according to demographic data (n = 34)

	No.	**%**
Sex		
Male	13	38.2
Female	21	61.8
Age (years)		
Min. – Max.	0.33 – 18.0	
Mean ± SD.	8.22 ± 4.22	
Median (IQR)	9.0 (6.0 – 12.0)	
Weight (kg)		
Min. – Max.	5.0 – 45.0	
Mean ± SD.	21.26 ± 9.82	
Median (IQR)	20.0 (15.0 – 28.0)	
Height (cm)		
Min. – Max.	60.0 – 150.0	
Mean ± SD.	113.03 ± 23.46	
Median (IQR)C	115.0 (105.0 – 131.0)	
BMI (kg/m^2)		
Min. – Max.	10.55 – 27.29	
Mean ± SD.	15.62 ± 3.49	
Median (IQR)	15.63 (13.89 – 17.10)	

Descriptive analysis of the studied cases according to baseline characteristics of different parameters

- **Echocardiography**

Table (2) demonstrates the echocardiographic parameters obtained during the initial assessment of cases. Estimated systolic pulmonary artery pressure (ESPAP) ranged from 45.0mmHg – 164.0 mmHg with the mean pressure 67.80 ± 27.40mmHg. Estimated diastolic pulmonary artery pressure (EDPAP) during the initial assessment ranged from 13 mmHg 61 mmHg with the mean pressure 31.61 ± 12.41mmHg. Main pulmonary artery (MPA) diameter ranged from 1.10 – 2.80 cm with the mean diameter 1.98 ± 0.47 cm. Right atrial area (RA) mean diameter was 9.51 ± 6.17 cm2. The mean Tricuspid Annular Plane Systolic Excursion (TAPSE) was 1.60 ± 0.44 cm. The mean Right ventricular outflow tract (RVOT) acceleration time was 88.88 ± 22.17 msec.

- **Cardiac magnetic resonance imaging parameters**

Right side parameters: ***Table (2)*** demonstrates the cardiac magnetic resonance imaging metrics in the right side during the initial assessment. We had 32 studied cases underwent cardiac MRI at the initial assessment. Cardiac MRI metrics included right ventricular ejection fraction (RVEF), right ventricular end diastolic volume (RVEDV), right ventricular end systolic volume (RVESV) and right ventricular stroke volume (RVSV) and indexed volumes.

During the initial assessment, the mean FVEF was 50.33 ± 9.30%. The mean RVEDV was 76.87 ±

43.98 ml. The mean RVESV was 39.73 ± 32.81ml. The mean RVSV was 36.59 ± 15.54ml. Regarding the RVEDV index, the mean was 96.33 ± 36.86 ml/m2. While the RVEDSV index, the mean was 49.35 ± 30.48ml/m2. Regarding the RVSV index, the mean was 46.90 ± 11.62I/min/m2.

Left side parameters: Cardiac magnetic resonance imaging metrics on the left side included; left ventricular ejection fraction (LVEF), left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV) and left ventricular stroke volume (LVSV).

During the initial assessment, the mean LVEF was 59.04 ± 5.85%. The mean LVEDV was 59.63 ± 26.53 ml while the mean LVESV 25.14 ± 12.45 ml. The mean LVEDV index 76.08 ± 23.26 ml/m2

Speckle tracking Doppler

Table (2) shows the parameters done in the speckle tracking Doppler during the initial assessment of cases. It revealed the mean global longitudinal strain (GLS) was -14.85 ± 4.28. The mean right ventricular ejection fraction (RVEF) was 46.03 ± 9.32 %.

- **Pro BNP level**

Table (2) shows the levels of pro brain natriuretic peptide (Pro BNP) obtained from the studied cases during the initial assessment. It ranged from 20.0 pg/ml to7715.7pg/ml and the mean level was 883.2 ± 1865.4 pg/ml.

- **6MWT value**

Table (2) shows the value of 6MWT during the initial assessment of case. It ranged from 40.0 m in severe uncontrolled cases to 550.0 m in mild cases with the mean value 342.95 ± 157.26 m.

Table (2): Descriptive analysis of the studied cases according to baseline characteristics of different parameters

	Min. – Max.	Mean ± SD.	Median (IQR)
ECHO data (n = 34)			
TR velocity (m/sec)	2.50 – 6.22	3.69 ± 0.88	3.25 (3.2 – 4.0)
ESPAP (mmHg)	45.0 – 164.0	67.80 ± 27.40	55.0 (50.0 – 75.7)
PR velocity (m/sec)	0.22 – 3.91	2.20 ± 0.79	2.10 (1.8 – 2.6)
EDPAP (mmHg)	13.0 – 61.0	31.61 ± 12.41	29.0 (23.0 – 37.0)
MPA diameter (cm)	1.10 – 2.80	1.98 ± 0.47	2.0 (1.7 – 2.3)
MPA Z score	-1.40 – 4.30	1.11 ± 1.41	0.85 (0.40 – 2.1)
RV/LV (cm)	0.41 – 2.0	0.78 ± 0.39	0.63 (0.50 – 0.90)
RVEDD Z score	-0.70 – 3.27	1.24 ± 1.14	1.10 (0.20 – 2.33)
RA area (cm^2)	3.10 – 38.0	9.51 ± 6.17	8.35 (6.2 – 10.2)
RA area Z score	-1.70 – 7.80	1.24 ± 2.11	0.80 (0.0 – 2.2)
TAPSE (cm)	0.70 – 2.70	1.60 ± 0.44	1.50 (1.4 – 1.8)
RVOT acceleration time (sec)	55.0 – 170.0	88.88 ± 22.17	89.0 (75.0 – 100.0)
Cardiac MRI of the Right ventricle (n = 32)			
RVEF (%)	24.0 – 64.0	50.33 ± 9.30	50.90 (42.0 – 59.5)
RVEDV (ml)	20.0 – 242.0	76.87 ± 43.98	71.40 (39.3 – 100.0)
RVESV (ml)	8.0 – 184.0	39.73 ± 32.81	29.0 (19.0 – 54.9)
RVSV (ml)	10.40 – 65.0	36.59 ± 15.54	38.90 (23.0 – 49.3)
RVEDVI (ml/m^2)	40.70 – 242.0	96.33 ± 36.86	89.50 (77.0 – 109.8)
RVESVI (ml/m^2)	13.50 – 184.0	49.35 ± 30.48	43.40 (33.2 – 59.1)
RVSVI ($I/min/m^2$)	27.20 – 83.50	46.90 ± 11.62	44.25 (39.3 – 57.7)
Cardiac MRI of the left ventricle (n = 32)			
LVEF (%)	47.0 – 71.30	59.04 ± 5.85	59.0 (55.0 – 62.0)
LVEDV (ml)	10.0 – 110.0	59.63 ± 26.53	63.15 (40.3 – 75.5)
LVESV (ml)	3.0 – 58.0	25.14 ± 12.45	25.0 (18.2 – 32.8)
LVSV (ml)	7.0 – 66.0	34.51 ± 15.24	37.50 (22.0 – 45.5)
LVEDVI (ml/m^2)	33.30 – 159.60	76.08 ± 23.26	72.0 (60.6 – 89.0)
LVESVI (ml/m^2)	10.0 – 77.70	32.62 ± 12.65	31.0 (24.5 – 38.2)
LVSVI ($I/min/m^2$)	23.30 – 81.90	43.48 ± 12.62	40.85 (34.5 – 50.8)
Flow Assessment (n = 32)			
MPA			
Net flow (ml)	6.0 – 65.0	32.60 ± 14.37	34.0 (22.0 – 41.8)
Forward flow (ml)	6.10 – 65.0	32.88 ± 14.36	36.50 (22.0 – 41.9)
Backward flow (ml)	0.0 – 3.0	0.28 ± 0.76	0.0 (0.0 – 0.05)
Regurge fraction (%)	0.0 – 9.0	1.01 ± 2.53	0.0 (0.0 – 0.10)

Aorta			
Net flow (ml)	7.0 – 67.0	32.95 ± 14.53	33.50 (21.5 – 44.7)
Forward flow (ml)	11.0 – 67.0	33.58 ± 14.03	33.50 (22.0 – 45.3)
Backward flow (ml)	0.0 – 4.0	0.19 ± 0.74	0.0 (0.0 – 0.0)
Regurge fraction (%)	0.0 – 8.0	0.44 ± 1.54	0.0 (0.0 – 0.0)
Speckle tracking Doppler (n = 34)			
GLS	-22.0 – -7.30	-14.85 ± 4.28	-14.25 (-18.2 – 12.2)
RVEDV	15.0 – 88.0	46.38 ± 17.71	45.0 (39.0 – 58.0)
RVESV	8.0 – 62.0	24.76 ± 11.12	25.0 (19.0 – 28.0)
RVEF (%)	16.0 – 57.0	46.03 ± 9.32	47.50 (42.0 – 53.0)
Pro-BNP (pg/ml) (n = 34)	20.0 – 7715.7	883.2 ± 1865.4	234.3 (45.0 – 500.0)
6 MWT Value (m) (n = 21)	40.0 – 550.0	342.95 ± 157.26	360.0 (250.0 – 480.0)

Cardiac Magnetic Resonance Imaging Metrics

Right side parameters:

Table (3) demonstrates the cardiac magnetic resonance imaging metrics in the right side during the initial assessment and the follow up. There is a statistically significant difference regarding right ventricular end diastolic volume (RVEDV) with higher mean at the follow up and P value 0.022. Also, there is statistically significant difference regarding right ventricular end systolic volume (RVESV) with higher mean at the follow up and P value 0.030 and also right ventricular stroke volume (RVSV) with the median 39.1 (29.2-50.8) at the follow up and P value 0.043. There is no statistically significant difference between the 2 groups regarding the indexed volumes.

Table (3): Comparison between Before and Follow up according to Cardiac MRI parameters in the Right side.

Cardiac MRI in Right	Before (n = 24)	Follow up (n = 24)	Test of Sig.	P
RVEF (%)				
Min. – Max.	36.50 – 64.0	28.0 – 65.0	t= 0.235	0.816
Mean ± SD.	51.03 ± 8.26	51.25 ± 9.42		
Median (IQR)	50.90 (43.50 – 59.50)	52.0 (47.0 – 56.5)		
RVEDV (ml)				
Min. – Max.	20.0 – 133.0	19.0 – 140.0	Z= 2.298*	0.022*
Mean ± SD.	75.59 ± 30.38	80.84 ± 35.13		
Median (IQR)	76.90 (52.0 – 98.55)	78.0 (59.4 – 104.5)		
RVESV (ml)				
Min. – Max.	9.60 – 81.0	10.0 – 100.2	Z= 2.176*	0.030*
Mean ± SD.	36.93 ± 19.33	41.50 ± 24.11		
Median (IQR)	31.0 (22.0 – 54.25)	33.50 (24.9 – 54.2)		
RVSV (ml)				
Min. – Max.	10.40 – 65.0	10.0 – 63.0	t= 2.138*	0.043*
Mean ± SD.	37.93 ± 14.37	39.37 ± 14.74		
Median (IQR)	40.0 (27.35 – 49.25)	39.10 (29.2 – 50.8)		
RVEDVI (ml/m^2)				
Min. – Max.	55.0 – 143.0	49.40 – 185.60	Z= 0.244	0.808
Mean ± SD.	90.51 ± 21.42	92.32 ± 26.91		
Median (IQR)	88.75 (77.0 – 103.5)	86.50 (75.5 – 104.3)		
RVESVI (ml/m^2)				
Min. – Max.	16.50 – 83.0	22.80 – 133.40	Z= 0.542	0.588
Mean ± SD.	44.41 ± 16.91	47.29 ± 23.03		
Median (IQR)	43.40 (33.15 – 52.25)	41.50 (35.2 – 52.0)		
RVSVI (I/min/m^2)				
Min. – Max.	31.50 – 65.0	26.60 – 60.0	t= 1.265	0.219
Mean ± SD.	46.12 ± 9.42	44.87 ± 9.32		
Median (IQR)	44.25 (39.25 – 55.15)	45.0 (39.0 – 52.0)		

IQR: Inter quartile range; SD: Standard deviation; t: Paired t-test; Z: Wilcoxon signed ranks test; p: p value for comparing between Before and Follow up; *: Statistically significant at $p \leq 0.05$.

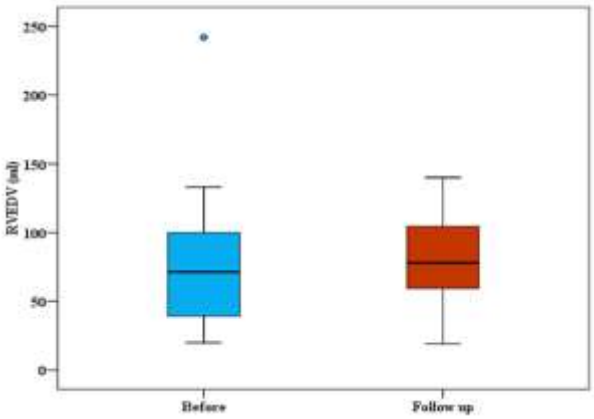

Figure (1): Comparison between before and follow up according to RVEDV in right side.

Left side parameters:

There is statistically significant difference between the initial and the follow up group regarding the left ventricular end diastolic volume (LVEDV) with higher mean value at the follow up 63.46 ± 22.02 and P value 0.025. Also, there is statistically significant difference regarding the left ventricular end systolic volume (LVESV) with mean 26.85 ± 9.26 at the follow up and P value 0.021. There is no statistically significant difference regarding the other indices.

Table (4): Comparison between Before and Follow up according to Cardiac MRI in Left side

Cardiac MRI in left	Before (n = 24)	Follow up (n = 24)	Test of Sig.	P
LVEF (%)				
Min. – Max.	52.0 – 70.0	50.0 – 63.0	**t= 0.813**	**0.424**
Mean ± SD.	58.53 ± 4.87	57.95 ± 3.38		
Median (IQR)	58.15 (55.0 – 61.85)	58.0 (55.0 – 60.0)		
LVEDV (ml)				
Min. – Max.	19.30 – 99.0	19.0 – 102.0	**Z= 2.245***	**0.025***
Mean ± SD.	61.39 ± 21.77	63.46 ± 22.02		
Median (IQR)	65.15 (43.50 – 75.50)	65.0 (48.1 – 80.0)		
LVESV (ml)				
Min. – Max.	8.0 – 40.0	8.0 – 42.0	**Z= 2.301***	**0.021***
Mean ± SD.	25.53 ± 8.65	26.85 ± 9.26		
Median (IQR)	26.0 (19.0 – 32.80)	27.0 (20.3 – 33.8)		
LVSV (ml)				
Min. – Max.	11.30 – 66.0	11.0 – 61.20	**t= 1.959**	**0.062**
Mean ± SD.	35.87 ± 14.13	36.88 ± 13.58		
Median (IQR)	38.70 (24.40 – 45.50)	40.0 (26.8 – 47.0)		
LVEDVI (ml/m^2)				
Min. – Max.	49.20 – 99.0	49.66 – 95.0	**Z= 1.492**	**0.136**
Mean ± SD.	75.15 ± 13.76	73.26 ± 12.33		
Median (IQR)	72.0 (66.10 – 87.0)	69.50 (65.8 – 83.0)		
LVESVI (ml/m^2)				
Min. – Max.	22.10 – 47.0	20.10 – 47.10	**Z= 0.939**	**0.348**
Mean ± SD.	32.28 ± 6.87	31.75 ± 6.53		
Median (IQR)	32.50 (25.75 – 38.20)	30.50 (26.3 – 36.6)		
LVSVI (I/min/m^2)				
Min. – Max.	27.10 – 66.0	29.56 – 60.10	t= 1.120	0.274
Mean ± SD.	42.90 ± 10.06	41.76 ± 9.07		
Median (IQR)	40.85 (36.0 – 50.30)	39.0 (36.3 – 47.5)		

IQR: Inter quartile range; SD: Standard deviation; t: Paired t-test; Z: Wilcoxon signed ranks test
p: p value for comparing between Before and Follow up; *: Statistically significant at $p \leq 0.05$.

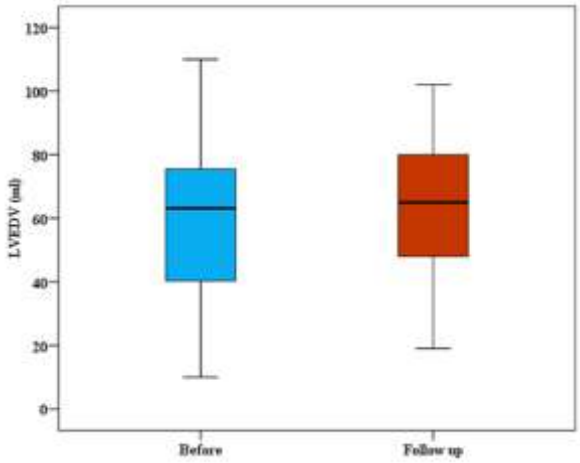

Figure (2): Comparison between before and follow up according to LVEDV in left side

CORRELATIONS

In table 6, right ventricular end systolic volume index (RVESVi) is positively correlated to the height (r=0.369 & p=0.038) and estimated systolic pulmonary artery pressure (ESPAP) (r=0.461 & p=0.008). But it is negatively correlated to right ventricular ejection fraction (RVEF) in the speckle tracking Doppler (r=0.666 & p<0.001).

There is positive correlation between RV ejection fraction (RVEF) by CMR and RVOT acceleration time obtained by echo (r=0.442 & p=0.011) and RV ejection fraction obtained by speckle tracking Doppler (r=0.795& p <0.001). But RVEF by CMR is negatively correlated to ESPAP (r=-0.522 & p=0.002) and GLS in the speckle Doppler (r=-0.412 & p=0.019).

Table (5): Correlation between initial cardiac MRI indices with demographic data (n = 32):

	Initial cardiac MRI indices					
	RVESVI (ml/m^2)		**LVEDVI (ml/m^2)**		**RVEF (%)**	
	r_s	**P**	**r_s**	**P**	**R**	**P**
WHO Class	0.198	0.278	-0.277	0.125	-0.320	0.074
Age (/years)	0.285	0.114	0.071	0.700	-0.181	0.322
Weight (kg)	0.349	0.051	0.167	0.360	-0.137	0.454
Height (cm)	0.369	0.038*	0.146	0.426	-0.202	0.267
BMI (kg/m^2)	0.030	0.869	0.009	0.961	0.100	0.584
Echo parameter						
ESPAP (mmHg)	0.461	0.008*	-0.174	0.341	-0.522	0.002*
RV/LV (cm)	0.265	0.142	-0.188	0.303	-0.268	0.138
TAPSE (cm)	-0.064	0.727	0.307	0.087	0.320	0.074
RVOT acceleration time (sec)	-0.286	0.112	0.224	0.217	0.442	0.011*
Speckle tracking Doppler						
GLS	0.324	0.070	-0.072	0.696	-0.412	0.019*
RVEF (%)	-0.666	<0.001*	0.002	0.993	0.795	<0.001*
Pro-BNP (pg/ml)	0.315	0.079	-0.047	0.798	-0.184	0.313
6 MWT Value (m) (n = 21)	-0.280	0.220	0.397	0.075	0.308	0.175

r: Pearson coefficient rs: Spearman coefficient *: Statistically significant at $p \leq 0.05$

- **Predictors of morbidity**

1-Right ventricular ejection fraction (RVEF%)

Linear regression analysis for the initial different parameters affecting the initial right ventricular ejection fraction (RVEF) obtained by cardiac MRI; revealed that there is statistically significant difference between RVEF% and the following risk factors:

1-O2 saturation (any increase in SPO2 will increase the RVEF% by 0.527 and p=0.05)

2-Estimated systolic pulmonary artery pressure (the higher the ESPAP, the lower RVEF by 0.172 and p=0.002)

3-Estimated diastolic pulmonary artery pressure (the higher the EDPAP, the lower RVEF by 0.374 and p=0.3)

4-Right ventricular dilatation (there is negative correlation with the RVEF% with B=-3.74, 95%CI and p=0.003)
5-Right atrial dilatation (negative correlation with B=-2.161, 95% CI and p=0.005).
6-Global longitudinal strain in speckle Doppler (B=-0.892, 95%CI and P=0.019).
7-Right ventricular ejection fraction in speckle Doppler (B=0.781, 95% CI and p <0.001).
By multivariate analysis of the different risk factors, there is statistically significant difference between the RV ejection fraction obtained by speckle Doppler and that of the CMR with p=0.001. There are no other detected risk factors statistically significant in our patients affecting RVEF% in cardiac MRI.

Table (6): Univariate and multivariate linear regression analysis for the initial different parameters affecting Initial RVEF (%) (n = 32)

	Univariate		**#Multivariate**	
	p	**B (LL – UL 95%C.I)**	**p**	**B (LL – UL 95%C. I)**
Increasing in **WHO Class**	0.074	-3.422 (-7.199 – 0.356)		
Presence of **Cyanosis**	0.295	-4.478(-13.065 – 4.109)		
Signs				
RR	0.384	-0.183 (-0.604 – 0.239)		
SPO_2	0.005*	0.527 (0.174 – 0.881)	0.130	0.234 (-0.074 – 0.543)
Male	0.359	3.168 (-3.785 – 10.121)		
Female	0.359	-3.168 (-10.121 – 3.785)		
Age (/years)	0.322	-0.400 (-1.213 – 0.412)		
Weight (kg)	0.454	-0.127 (-0.467 – 0.214)		
Height (cm)	0.267	-0.079 (-0.223 – 0.064)		
BMI (kg/m^2)	0.584	0.266 (-0.717 – 1.250)		
Pro-BNP (pg/ml)	0.313	-0.001 (-0.003 – 0.001)		
6 MWT Value (m) (n=21)	0.175	0.017 (-0.008 – 0.043)		
Echo parameter				
ESPAP (mmHg)	0.002*	-0.172 (-0.277 – -0.067)	0.213	-0.091 (-0.237 – 0.056)
TAPSE (cm)	0.074	6.815 (-0.709 – 14.339)		
RVEDD Z score	0.010*	-3.782 (-6.586 – -0.979)	0.522	1.007 (-2.192 – 4.206)
EDPAP (mmHg)	0.003*	-0.374 (-0.611 – -0.136)	0.857	0.030 (-0.312 – 0.372)
RA area Z score	0.005*	-2.161 (-3.605 – -0.718)	0.269	-0.256 (-0.724 – 0.211)
Speckle tracking Doppler				
GLS	0.019*	-0.892 (-1.629 – -0.156)	0.576	0.204 (-0.538 – 0.946)
RVEF (%)	<0.001*	0.781 (0.559 – 1.003)	0.001*	0.599 (0.260 – 0.938)

B: Unstandardized Coefficients; C.I: Confidence interval; LL: Lower limit; UL: Upper Limit; #: All variables with p<0.05 was included in the multivariate; *: Statistically significant at $p \leq 0.05$

2-Right ventricular end systolic volume index (RVESVi)
Univariate linear regression analysis for the initial different parameters affecting the initial RVESV index revealed the following risk factors:
1-O2 saturation (negative correlation with RVESV index with B= -1.900, 95% CI and P=0.002)
2-Right ventricular dilatation (positive correlation with B=13.857, 95% CI and p=0.003)
3-Right atrial dilatation (positive correlation with B=9.325, 95% CI and p<0.001)
4-Global longitudinal strain (positive correlation with B=3.074, 95% CI and p=0.013)
5-Right ventricular ejection fraction (negative correlation with B=-2.437, 95% CI and p<0.001).
Multivariate analysis revealed statistical significant difference with o2 saturation (B=-0.973, 95% CI and p=0.047) and right ventricular ejection fraction by speckle Doppler (B=-1.867 95% CI and p<0.001).

Table (7): Univariate and multivariate linear regression analysis for the initial different parameters affecting Initial RVESVI (ml/m2) (n = 32)

	Univariate		#Multivariate	
	p	**B (LL – UL 95%C. I)**	**p**	**B (LL – UL 95%C. I)**
Increasing in **WHO Class**	0.111	10.057 (-2.454 – 22.568)		
Presence of **Cyanosis**	0.359	12.899 (-15.352 – 41.150)		
Signs				
RR	0.247	0.791 (-0.578 – 2.159)		
SPO_2	0.002*	-1.900 (-3.021 – -0.779)	0.047*	-0.973 (-1.930 – -0.016)
Male	0.725	-4.008 (-27.064 – 19.048)		
Female	0.725	4.008 (-19.048 – 27.064)		
Age (/years)	0.253	1.511 (-1.137 – 4.158)		
Weight (kg)	0.261	0.618 (-0.485 – 1.722)		
Height (cm)	0.165	0.323 (-0.141 – 0.788)		
BMI (kg/m^2)	0.873	0.256 (-2.980 – 3.493)		
Pro-BNP (pg/ml)	0.150	0.004 (-0.002 – 0.010)		
6 MWT Value (m) (n=21)	0.416	-0.022 (-0.077 – 0.033)		
Echo parameter				
ESPAP (mmHg)	0.100	0.319 (-0.065 – 0.703)		
TAPSE (cm)	0.553	-7.600 (-33.463 – 18.262)		
RVEDD Z score	0.003*	13.857 (4.969 – 22.746)	0.635	-2.633 (-13.893 – 8.627)
EDPAP (mmHg)	0.118	0.681 (-0.184 – 1.546)		
RA area Z score	<0.001*	9.325 (5.171 13.479)	0.068	4.571 (-0.355 – 9.497)
Speckle tracking Doppler				
GLS	0.013*	3.074 (0.689 – 5.460)	0.541	-0.733 (-3.164 – 1.698)
RVEF (%)	<0.001*	-2.437 (-3.221 – -1.653)	<0.001*	-1.867 (-2.794 – -0.939)

B: Unstandardized Coefficients; C.I: Confidence interval; LL: Lower limit; UL: Upper Limit; #: All variables with $p<0.05$ was included in the multivariate; *: Statistically significant at $p \leq 0.05$

3-Left ventricular end diastolic volume index (LVEDVi)

Uni-variate linear regression analysis for the initial different parameters affecting the initial LV end diastolic volume index revealed that there is only statistically significant difference with 6MWT value (B= 0.051, 95% CI and p=0.027)

No other risk factors detected as statistically significant in our patients.

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Table (8): Univariate linear regression analysis for the initial different parameters affecting initial LVEDVI (ml/m2) (n = 32)

	Univariate	
	P	**B (LL – UL 95%C.I)**
Increasing in **WHO Class**	0.893	-0.665 (-10.632 – 9.302)
Presence of **Cyanosis**	0.549	-6.460 (-28.202 – 15.282)
Signs		
RR	0.591	-0.283 (-1.347 – 0.780)
SPO_2	0.545	-0.301 (-1.307 – 0.704)
Male	0.285	9.212 (-8.087 – 26.510)
Female	0.285	-9.212 (-26.510 – 8.087)
Age (/years)	0.702	0.389 (-1.672 – 2.450)
Weight (kg)	0.545	0.256 (-0.599 – 1.111)
Height (cm)	0.340	0.171 (-0.189 – 0.532)
BMI (kg/m^2)	0.760	0.372 (-2.095 – 2.840)
Pro-BNP (pg/ml)	0.416	0.002 (-0.003 – 0.006)
6 MWT Value (m) (n=21)	0.027*	0.051 (0.006 – 0.095)
Echo parameter		
ESPAP (mmHg)	0.166	-0.206 (-0.504 – 0.091)

TAPSE (cm)	0.276	10.586 (-8.878 – 30.049)
RVEDD Z score	0.245	4.454 (-3.216 – 12.125)
EDPAP (mmHg)	0.206	-0.423 (-1.093 – 0.246)
RA area Z score	0.515	1.325 (-2.780 – 5.431)
Speckle tracking Doppler		
GLS	0.502	0.668 (-1.337 – 2.672)
RVEF (%)	0.582	-0.248 (-1.160 – 0.663)

B: Unstandardized Coefficients
C.I: Confidence interval LL: Lower limit UL: Upper Limit
*: Statistically significant at $p \leq 0.05$

- **Predictors of mortality**

The cut off value of predictors of mortality in our study can't be obtained due to small sample size as shown in figure 1. Table 33 explain prognostic performance for initial cardiac MRI indices to predict mortality.

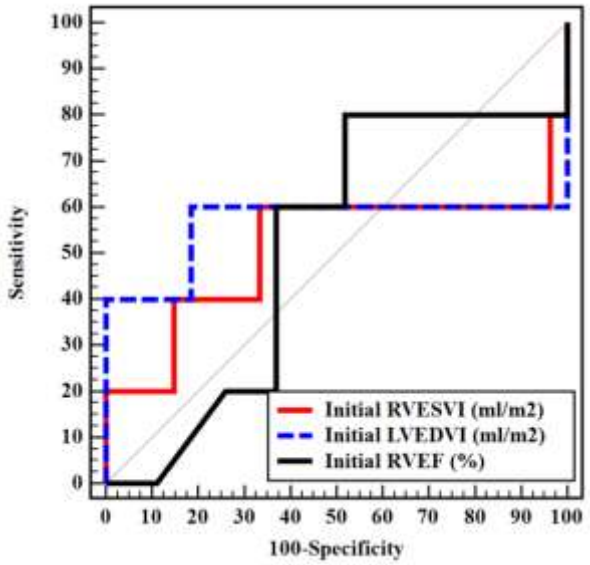

Figure (3): ROC curve for initial cardiac MRI indices to predict mortality (n= 5 vs. 27)

4. DISCUSSION

Interstitial (diffuse) lung diseases in infants and children comprise a rare heterogeneous group of parenchymal lung disorders, with clinical symptoms characterized by dyspnea, tachypnea, crackles, and hypoxemia. They arise from a wide spectrum of developmental, genetic, inflammatory, infectious, and reactive disorders **(Lee, 2018).**

Pulmonary hypertension is defined as a resting mean pulmonary arterial pressure of greater than or equal to 25 mm Hg at right-sided heart catheterization. If left undiagnosed and untreated, PH progresses to right ventricular dilatation and hypertrophy with subsequent heart failure, followed by death **(Hoeper, 2009).**

While cardiac right heart catheterization (RHC) remains the gold standard and mandatory for establishing the diagnosis of PH, non-invasive imaging of the heart plays a central role in the diagnosis and management of all forms of PH. Although Doppler echocardiography (ECHO) can measure a range of hemodynamic and anatomical variables, it has limited utility for visualization of the pulmonary artery and, oftentimes, the right ventricle. Cardiovascular magnetic resonance (CMR) provides comprehensive information about the anatomical and functional aspects of the pulmonary artery and right ventricle that are of prognostic significance for assessment of long-term outcomes in disease progression **(Aryal et al., 2020).**

This current study was prospective cohort study that was conducted on 34 cases with 13 males (38.2 %) and 21 females (61.8%). The median age was 9 years old with IQR from (6-12).

In our study we had 20 cases (58.8%) were diagnosed as interstitial lung disease due to native parenchymal lung disorder and the other 14 cases (41.2%) were due to secondary systemic disorder. This is matched with a study done by **(Behr and Ryu, 2008) and (Deutch et al., 2007)** that assessed the prevalence of pulmonary hypertension in different ILD groups.

Ten studies presented data on the occurrence of pulmonary hypertension in childhood interstitial lung disease **(Fan et al., 2015).**

Echocardiography (Echo), Cardiac Magnetic Resonance Imaging (CMR), speckle tracking Doppler, pro brain natriuretic peptide (pro-BNP) and 6-minute walk test (6MWT) were done to all patient at the initial assessment and follow up after 6 months

Our study concentrated on the cardiac MRI derived metrics to assess the right ventricular function in childhood ILD patients complicated with pulmonary hypertension. Thresholds derived from Cardiac MRI metrics included: Right ventricular end systolic volume index (RVESVi), Left ventricular end diastolic volume index (LVEDVi) and right ventricular ejection fraction (RVEF). During the initial assessment, the median RVEF was 50.90 (43.50-59.50) %, the mean RVESV index was 44.41 ± 16.91 ml/m2 and the mean LVEDV index was 75.15 ± 13.76 ml/m2. During the follow up after 6 months, the median RVEF was 52.0 (47-56.5) %, RVESV index 47.29 ± 23.03 ml/m2 and LVEDV index 73.26 ± 12.33 ml/m2. There was no statistically significant difference between the initial and the follow up groups regarding the indexed volumes.

This is matched with a study done in 2020 that identified Cardiac magnetic resonance imaging thresholds for risk stratification in pulmonary hypertension. These thresholds included Right ventricular end systolic volume index (RVESVi), left ventricular end diastolic volume index (LVEDVi) and right ventricular ejection fraction (RVEF) **(Lewis et al., 2020).**

By correlating the 3 CMR indices with other parameters, it revealed that RVESV index was positively correlated to the height (r=0.369 & p=0.038) as the indexed volume differs according to body surface area. Moreover, RVESVi was positively correlated to the estimated systolic pulmonary artery pressure (ESPAP) (r=0.461& p=0.008) but it is negatively correlated to RVEF obtained by speckle tracking Doppler (r=0.666 & p<0.001). This could be explained that the rise in the systolic pulmonary pressure results in right ventricular dilatation.

This is matched with a cohort study done at 2019 that assessed the correlation of Cardiac MRI metrics to estimated systolic pulmonary artery pressure and revealed that cardiac MRI metrics have high diagnostic accuracy in patients suspected of having pulmonary hypertension **(Johns et al., 2019).**

Moreover, there was positive correlation between RVEF by CMR and RVOT acceleration time by echo (r=0.442 & p=0.011) and RV ejection fraction obtained by speckle tracking Doppler (r=0.795& p <0.001). But RVEF by CMR was negatively correlated to ESPAP (r=-0.522 & p=0.002) and GLS in the speckle Doppler (r=-0.412 & p=0.019).

This could be explained that the rise in the pulmonary artery pressure results in decrease in the RV systolic function and elevation of afterload that could be one of the main mechanisms of RV systolic dysfunction (RVSD) in ILD patients.

All these correlations were matched with a study done by **Kato et al**. who demonstrated that right ventricular systolic dysfunction (RVSD) in ILD patients can be clearly detected by cine CMR **(Kato et al., 2015)**

Uni-variate linear regression analysis for the initial different parameters affecting the initial right ventricular ejection fraction (RVEF) obtained by cardiac MRI; revealed that right ventricular ejection fraction is affected by the following factors:

1. O2 saturation (any increase in SPO2 will increase the RVEF% by 0.527 and p=0.05).
2. Estimated systolic pulmonary artery pressure (the higher the ESPAP, the lower RVEF by 0.172 and p=0.002)
3. Estimated diastolic pulmonary artery pressure (the higher the EDPAP, the lower RVEF by 0.374 and p=0.3)
4. Right ventricular dilatation (there is negative correlation with the RVEF% with B=-3.74, 95%CI and p=0.003)
5. Right atrial dilatation (negative correlation with B=-2.161, 95% CI and p=0.005)
6. Global longitudinal strain in speckle Doppler (there was negative correlation and B=-0.892, 95%CI and P=0.019)
7. Right ventricular ejection fraction in speckle Doppler (there was positive correlation and B=0.781, 95% CI and p <0.001).

By multivariate analysis of the different risk factors, there was statistically significant difference between the RV ejection fraction obtained by speckle Doppler and that of the CMR with p=0.001. There were no other detected risk factors statistically significant in our patients affecting RVEF% in cardiac MRI.

These come with agreement with the study done by Kato et al who showed that RVEF was negatively correlated with mean pulmonary artery pressure (r =0.32, p=0.017) **(Kato et al., 2015).**

Univariate linear regression analysis for the initial different parameters affecting the initial right ventricular end systolic volume index (RVESVi) revealed the following risk factors:

1. O2 saturation (negative correlation with RVESV index with B= -1.900, 95% CI and P=0.002) this means that when O2 saturation is low results in right ventricular dilatation by 1.900.
2. Right ventricular dilatation by echocardiography (positive correlation with B=13.857, 95% CI and p=0.003)
3. Right atrial dilatation by echocardiography (positive correlation with B=9.325, 95% CI and p<0.001)
4. Global longitudinal strain (positive correlation with B=3.074, 95% CI and p=0.013)

5. Right ventricular ejection fraction by speckle tracking Doppler (negative correlation with B=-2.437, 95% CI and p<0.001).

Multivariate analysis revealed statistically significant difference with o2 saturation (B=-0.973, 95% CI and p=0.047) and right ventricular ejection fraction by speckle Doppler (B=-1.867 95% CI and p<0.001).

This comes in agreement with a study done at 2020 that was conducted on pulmonary hypertensive patients and CMR was done. One of the thresholds that were obtained was right ventricular end systolic volume index (RVESVi) and percentage-predicted right ventricular end-systolic volume index that independently predicted outcome **(Lewis et al., 2020).**

Uni-variate linear regression analysis for the initial different parameters affecting the initial LV end diastolic volume index (LVEDVi) revealed that there is only statistically significant difference with 6MWT value (B= 0.051, 95% CI and p=0.027)

No other risk factors detected as a statistically significant in our patients.

To the best of our knowledge, this is the first investigation to evaluate the CMR derived RVEF in childhood ILD patients with pulmonary hypertension. During mean follow up of 6 months, we had 6 died cases due to ILD exacerbation and respiratory failure. One of them had severely impaired RVEF (24%) with severe pulmonary hypertension (ESPAP= 80mmHg). The other 5 cases had mild impairment of RV systolic function (RVEF % between 45-55%) with moderate to severe pulmonary hypertension. We had 7 cases that had worse outcome (higher PAP, lower SO2, lower RVEF %, higher RVESVi and lower 6MWD). But in our study, we didn't determine the cut off value of predictors of mortality due to small sample size (AUC=0.511- p=0.938).

Kato et al demonstrated the prognostic value of RVEF by CMR in ILD patient and showed that CMR derived RVEF (Hazard ratio= 0.889, 95% CI: 0.809 – 0.976, p = 0.014) were significant predictors of future events. In multivariate Cox regression analysis, CMR derived RVEF (Hazard ratio= 0.897, 95% CI: 0.810 – 0.992, (p = 0.035) was the only independent predictor of future events **(Kato et al., 2015).**

There is another study done at 2017 that determined the value of magnetic resonance imaging (MRI) metrics for prediction of mortality in PAH and concluded that MRI measurements reflecting right ventricular structure and stiffness of the pulmonary vasculature are independent predictors of outcome in PAH. In combination with clinical data MRI has moderate prognostic accuracy in the evaluation of patients with PAH **(Swift et al., 2017).**

STUDY LIMITATION

1- This study was a single-center study and included a relatively limited number of patients.

2- The mean follow-up duration was about six months.

3- Although RVEF calculated by cine CMR is a non-invasive and useful index, CMR is problematic for patients with claustrophobia and the need for general anesthesia for younger children (<4 years) with very poor chest condition for sedation with careful monitoring of the vital signs.

5. CONCLUSION

1-Pulmonary hypertension (PH) is a well-recognized complication of interstitial lung diseases (ILD), which worsens prognosis and impairs exercise capacity.

2-Echocardiography is the most widely used, non-invasive method for pulmonary hypertension assessment in interstitial lung diseases.

3-Cardiac magnetic resonance imaging can be used in conjunction with the transthoracic echocardiography for assessment of pulmonary hypertension in pediatric interstitial lung disease.

4-Cardiac magnetic resonance imaging provides comprehensive information about the anatomical and functional aspects of the pulmonary artery and right ventricle that are of prognostic significance for assessment of long-term outcomes in disease progression.

Declaration of Conflicting of Interests

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