The Egyptian Journal of Hospital Medicine (October 2025) Vol. 101, Page 4807-4812

Impact of End-Stage Renal Disease on Ventilatory Function and Functional Capacity in Children

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ABSTRACT
Background: End-stage renal disease (ESRD) is the last stage of chronic kidney disease (CKD), as the kidneys are not able to function on their own. Children at this stage have deterioration in mechanical and ventilatory functions of the lungs as the air flow is affected by the drugs and hemodialysis. The physiology of the lung is also altered by the disease as it changes the fluid homeostasis, acid-base stability and tone of vessels. The disturbances in lung and hemodynamic causes changes in ventilatory regulation, pulmonary congestion, capillary stress-induced damage, and pulmonary vascular disorders.
Objective: This study aimed to detect the effect of CKD on lung functions and functional capacity and to investigate the relation between functional capacity and ventilatory functions in children at ESRD subjected to dialysis.
Methods: Twenty-one children at ESRD treated with dialysis with an age range from six to fifteen years were selected from Zagazig University Hospitals. They were subdivided according to their age into two groups (group 1 with age ranged from 6 to 10 years and group 2 with age range from eleven to fifteen years) in addition to twenty-one age-matched normal healthy children participated in the current study. Ventilatory functions and functional capacity were measured for all children by using a computerized spirometer and 6-minute walk test (6MWT) respectively.
Results: Bivariate Spearman correlation coefficients were computed between functional capacities with ventilatory functions for children in the age-matched groups. The results revealed a statistically significant positive correlation between functional capacity with ventilatory functions in both age strata in the normal group but in ESRD children, there was positive non-significant correlation between 6 MWT with ventilatory functions in both age strata. There was a statistically significant difference between the studied groups regarding the 6MWT, MVV, FVC, FEV1, and PEF (all were significantly higher among the normal group).
Conclusions: There was significantly positive correlation between ventilatory functions and functional capacity in normal children, while in ESRD children the correlation was not statistically significant.
Keywords: Children, ESRD, Functional capacity, Ventilatory functions.

INTRODUCTION
When kidney damage is present or a glomerular filtration rate (GFR) is less than 60 ml/min/1.73 m^2 for at least three months, it is referred to be CKD, which can lead to ESRD [1]. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) CKD was classified to five stages: Stage 1 with normal GFR ≥ 90 mL/min/1.73m^2 and persistent albuminuria, stage 2 with GFR of 60-89 mL/min/1.73m^2 and persistent albuminuria, stage 3 with GFR of 30-59 mL/min/1.73m^2, stage 4 with GFR of 15-29 mL/min/1.73m^2 and stage 5 with GFR of less than 15 mL/min/1.73m^2 or ESRD. Renal replacement is the treatment choice if the child's GFR is less than 30 mL/min/1.73 m^2 [2].

Chronic glomerulonephritis, steroid-resistant nephrotic syndrome, and renal ciliopathies account for almost 70% of all cases of CKD in children. Other causes may include nephrolithiasis/nephrocalcinosis, infectious and interstitial diseases, thrombotic microangiopathies, Wilms tumor and others [3].

ESRD adversely affects growth, psychosocial and emotional well-being, educational attainment, and patient-centered outcomes including quality of life [4]. Patients at ESRD suffer from a decrease in the mechanical and ventilatory functions of the lungs due to circulating toxins resulting from the renal uremia, increased fluid load, electrolyte imbalance, acid-base disturbance, immune response, malnutrition, anemia, drugs affection, and dialysis. Also, children at this stage may suffer from weakness of the respiratory muscles like the diaphragm and the intercostal muscles [5].

Patients at ESRD also suffer from muscle dysfunctions that may result from depletion of amino acids, chronic inflammation, muscle protein production and breakdown are not balanced, change in capillary perfusion and peripheral neuropathy that lead to atrophy in muscle fibers and decrease in the functional capacity [6]. Children at ESRD are less energetic than their peers and mostly dependent on their caregivers in the tasks associated with disease management like hospitalizations. Also, they have social challenges because they are unable to participate in peer-related activities and are unable to attend school regularly due to hospital visits [7, 8].

Because the children at ESRD have affection of their daily activities performance and due to the limitation of the literatures about the effect of ESRD on functional capacity and ventilatory functions, the current study was conducted to investigate the effect of ESRD on functional capacity and ventilatory functions and to determine the relation between ventilatory

Received: 02/05/2025
Accepted: 04/07/2025

functions and functional capacity in children of ESRD subjected to dialysis in comparison with normal peers.

PATIENTS AND METHODS

Twenty-one children at ESRD treated with dialysis with an age range from six to fifteen years were selected from Zagazig University Hospitals. They were subdivided according to their age into two groups (group 1 with age ranged from 6 to 10 years and group 2 with age range from eleven to fifteen years) in addition to twenty-one age matched normal healthy children participated in the current study.

Subjects: Based on previous studies and assuming a one-tail exact correlation bivariate normal model, a sample size of 42 participants was estimated to detect the effect of ESRD on ventilatory functions and functional capacity and detect the relations between these variables when compared to those of typically developing age matched healthy children. Assuming a significance level (α) of 0.05, power (1-β error probability) =0.80, Effect size f^2 (V) = 0.1764706, Pillai V = 0.3000 with 2 independent groups comparison for major dependent variables outcome (ventilatory functions and functional capacity). The calculation was performed using G Power program 3.1.9 and sample size calculations, version 3.1, for Microsoft Windows (Heinrich-Heine-University, Düsseldorf, Germany) for one tailed test.

Inclusion criteria: 1) Homeostasis stable, 2) could understand and obey commands and 3) subjected to hemodialysis 3 times per week that was started at least 1 year ago.

Exclusion criteria: 1) Respiratory distress, chronic pulmonary disease and tuberculosis, or arrhythmias, 2) acute chest infection and heart failure, or liver cirrhosis and 3) musculoskeletal or neurological disorders.

This study included twenty-one children of both sexes diagnosed as ESRD, who were subjected to renal dialysis in addition to twenty-one age-matched normal volunteers' healthy children with no history of medical disease were selected from Zagazig schools. Both diseased and normal participants were subdivided into two strata according to age, from six to ten years and from eleven to fifteen years as represented (Figure 1).

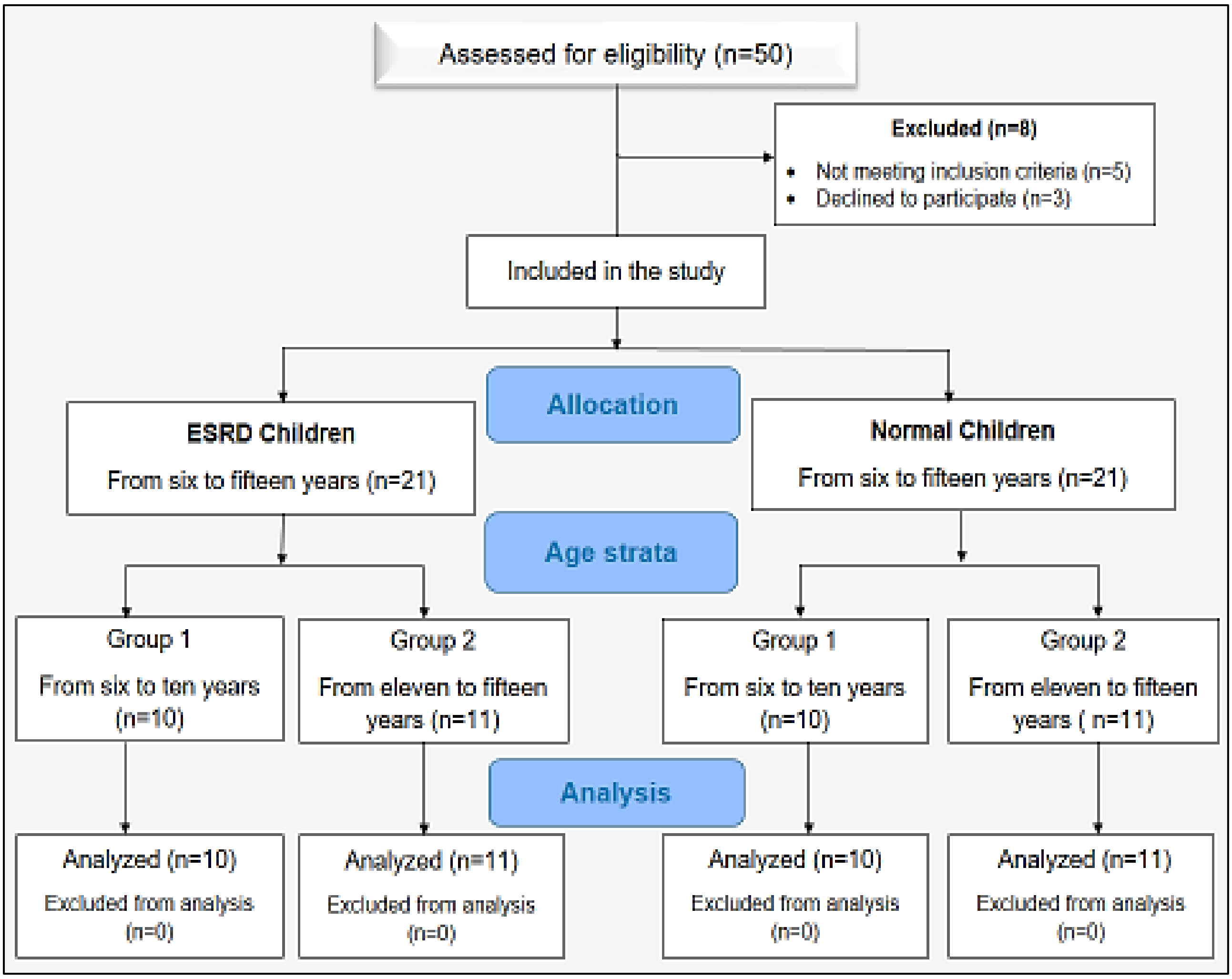

Fig. (1): The study flow chart.

Procedures: Evaluation of ventilatory functions was done using computerized spirometry (Spiro-spectrum version 2000–2013), which is a reliable and an inexpensive tool, used for the evaluation of ventilatory functions in children over 6 years [9]. Test steps were demonstrated to each child individually in simple terms before starting assessment. After recording each child's individualized data (name, age, sex, weight, and height), the child was instructed to maintain a sitting position according to the recommended standards. A nasal clip was then placed to prevent airflow through the nasal passage, followed by the placement of a mouthpiece.

The child was directed to firmly close their lips around the mouthpiece. Next, they were asked to take a full inspiration and then exhale as rapidly, forcefully, and completely as possible, followed by another full and rapid inspiration to assess forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and peak expiratory flow (PEF). Maximum voluntary ventilation (MVV) was measured by instructing the child to breathe through the spirometer as deeply, rapidly, and forcefully as possible for 12–15 seconds. The best value was obtained from at least three attempts, measured at 3-minute intervals [10].

Functional capacity was measured by using 6MWT, which is valid and reliable for the assessment of functional capacity in children [11].

It is low-cost and easy to perform as the therapist marked two points with a distance of 30 m between them then the child was asked to walk the greatest possible distance between the two points and make turn at the end point in a period of 6 min and the child was also instructed to stop at any time he /she feels discomfort on a wooden chair that was available beside the walkway [12].

Ethics approval: The study was conducted after it was approved by the Ethical Committee of Faculty of Physical Therapy, Cairo University (No: P.T. REC/004842). Written permission was obtained from the parents of each participant. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Version 25 for Windows of the statistical SPSS Package was used to do the statistical analysis. The Shapiro-Wilk test was used to confirm that the data were spread out properly. To compare the groups' weight, height, body mass index (BMI), and 6MWT, an independent t-test was used. When comparing the ventilatory functions (MVV, FEV1, FVC, and PEF) of the various groups, the Mann Whitney test was employed. Bivariate correlation, or the Spearman rank correlation coefficient was used to calculate the relationship and direction between the ventilatory functions and functional capacity in children with ESRD and normal children. The level of significance is defined at a P-value ≤ 0.05.

RESULTS

Children characteristics: Comparison of the demographic data including (weight, height & BMI), ventilatory functions and the 6MWT between the studied groups with different age strata group 1 from 6-10 years and group 2 from 11-15 years. There was statistically significant difference between the studied groups regarding weight, height, 6MWT, MVV, FEV1, FVC and PEF (all are significantly higher among normal group) within both age groups (group 1 and 2) while there was no significant difference between them regarding BMI (Table 1).

Table (1): Comparison of baseline characteristics between ESRD and normal children within different age strata

	Group 1 (6 – 10 years)			**Group 2 (11 – 15 years)**		
	ESRD group Mean ± SD	**Normal group Mean ± SD**	$p^{¥}$	**ESRD group Mean ± SD**	**Normal group Mean ± SD**	$p^{¥}$
Weight (kg)	20.8 ± 4.32	30.1 ± 7.46	0.003*	34.65 ± 11.69	45.8 ± 9.32	0.022*
Height (cm)	114.5 ± 11.17	132.8 ± 7.07	<0.001*	133.82 ± 10.45	153.73 ± 11.45	<0.001*
BMI (kg/m^2)	15.77 ± 1.9	16.92 ± 3.28	0.349 NS	18.86 ± 4.23	19.28 ± 3.23	0.797 NS
6MWT	214.0 ± 49.93	495.0 ± 32.83	<0.001*	241.82 ± 47.71	504.6 ± 25.05	<0.001*
	Median (IQR)	**Median (IQR)**	$P^{§}$	**Median (IQR)**	**Median (IQR)**	$P^{§}$
MVV	34.2(24.0 – 36.2)	41.3(28.4 – 47.7)	0.023*	62.4(59.8 –64.0)	81.5(74.6 – 95.2)	<0.001*
FVC	0.88(0.56 – 1.12)	1.37(0.96 – 1.55)	0.015*	2.57(1.83– 3.07)	3.16(2.78 – 4.01)	0.016*
FEV1	0.63(0.53 – 1.02)	1.37(0.96 – 1.53)	0.002*	2.54(1.81 –2.75)	3.16(2.78 – 3.73)	0.002*
PEF	1.54(1.01 – 1.76)	3.51(2.72 – 3.66)	<0.001*	4.95(4.13–5.18)	6.4(6.12 – 7.54)	<0.001*

§ Mann Whitney test, ¥independent sample t test, IQR: inter quartile range, *p<0.05 is statistically significant, NS: non-significant.

Bi-variate spearman rank correlation coefficients were computed between 6MWT with ventilatory functions for normal children at both age strata. There were statistically significant large positive correlations between 6MWT and ventilatory functions test of the normal children within different age groups (Table 2 and figures 2, 3, 4 & 5).

Table (2): Correlation between 6MWT and ventilatory functions test among normal children

	Normal Group 1 (6 – 10 years)		Normal Group 2 (11 – 15 years)	
	r	*p*	r	*p*
MVV	0.65	0.002*	0.799	<0.001*
FVC	0.667	<0.001*	0.625	0.002*
FEV_1	0.784	<0.001*	0.706	<0.001*
PEF	0.823	<0.001*	0.813	<0.001*

r: Spearman rank correlation coefficient *$p<0.05$ is statistically significant.

Bi-variate spearman rank correlation coefficients were computed between 6MWT with ventilatory functions for ESRD children at both age strata and showed positive correlations that are not statistically significant between 6MWT and ventilatory functions test of the studied ESRD children within different age groups (Table 3, Figures 2,3, 4, 5).

Table (3): Correlation between 6MWT and ventilatory functions test among studied ESRD children

	ESRD Group 1 (6 - 10 years)		ESRD Group 2 (11 – 15 years)	
	r	*p*	r	*p*
MVV	0.287	0.422	0.25	0.458
FVC	0.098	0.789	0.549	0.08
FEV1	0.303	0.395	0.472	0.142
PEF	0.384	0.273	0.259	0.441

r: Spearman rank correlation coefficient *$p<0.05$ is statistically significant

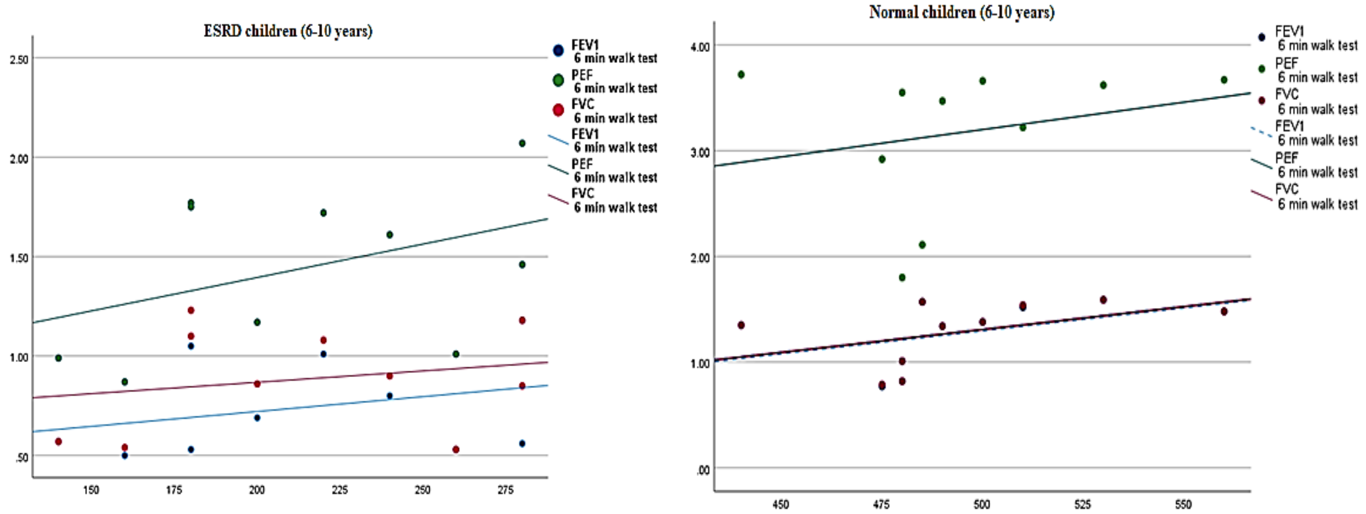

Fig. (2): Correlation between 6MWT and pulmonary function test within group 1 (ESRD and normal children).

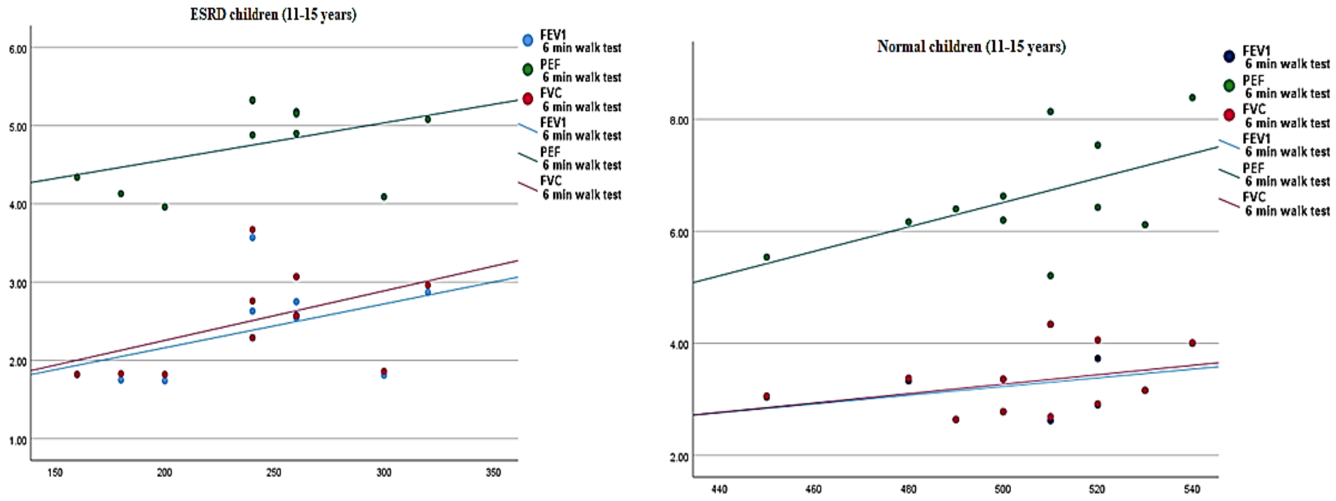

Fig. (3): Correlation between 6MWT and pulmonary function test within group 2 (ESRD and normal children).

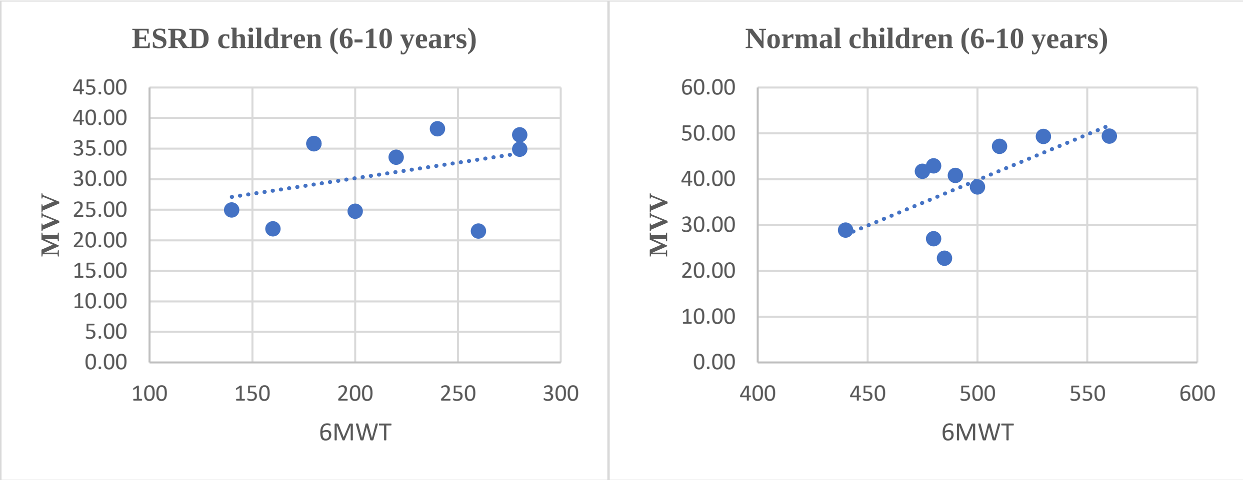

Fig. (4): Correlation between 6MWT and MVV within group 1 (ESRD and normal children).

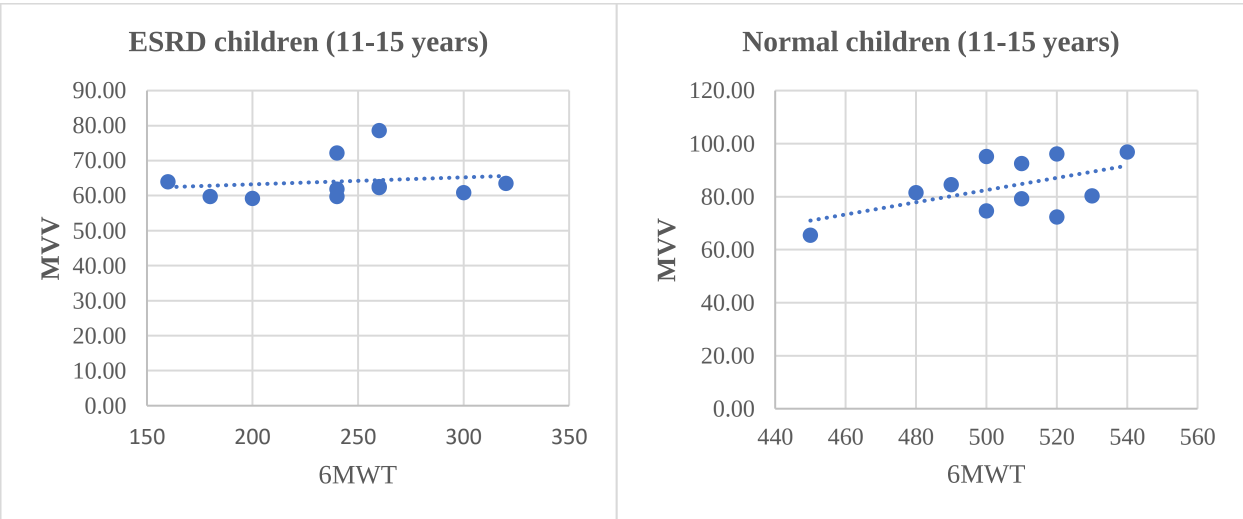

Fig. (5): Correlation between 6MWT and MVV within group 2 (ESRD and normal children).

DISCUSSION

The findings of the current study indicated that children with ESRD had lower mean values for weight, and height compared to their healthy peers. This discrepancy may be attributed to the prevalence of short stature among children with childhood-onset ESRD, probably brought on by metabolic and nutritional issues such anemia, uremia, metabolic acidosis, calcium and phosphorus imbalances, abnormalities in parathyroid hormone, and hormonal disorders. Children with ESRD who have growth failure are more likely to mortality and require hospitalization [4]. The current study comes in the same line with **Apostolou *et al.*** [13] who measured body weight and height of 30 children aged 1-16 years with CKD stages III & IV and their results found that children on peritoneal dialysis have lower height scores compared to their healthy peers as the height is the most reliable marker of growth and positively correlated to malnutrition while low growth rate was associated with disease stage in children with CKD. Also, **Hamasaki *et al.*** [14] investigated 447 children with CKD stages 3-5 in 113 Japanese medical facilities and discovered significant development impairment as compared to healthy children.

We also found that ESRD children had lower mean ventilatory function values (FEV1, FVC, PEF, MVV) and functional capacity than normal children, which could be explained by the fact that CKD causes uremic myopathy, resulting in dysfunction across multiple systems, including the musculoskeletal, cardiovascular, metabolic, and respiratory systems. In the musculoskeletal system, CKD contributes to lower protein-calorie intake, muscle protein imbalance, and muscular atrophy, mostly affecting type II muscle fibers. Additionally, it weakens the capillary and vascular beds, resulting in intravascular calcification that limits local blood flow and eventually lowers functional capability. By decreasing muscular strength, endurance, and lung capacity, the illness may also affect respiratory muscles, including the diaphragm and intercostals, which are also skeletal muscles [15]. This significant difference between normal and diseased patient regarding ventilatory functions is supported by studies done by **Afify *et al.*** [16] and **Takken *et al.*** [17] who examined the ventilatory functions in children and adolescents aged between 6-16 years with ESRD receiving regular hemodialysis and reported considerably decline in FEV1, FVC, PEF, MVV, and FEF in ESRD compared to controls of the same age. **Teixeira *et al.*** [18] found in their study a positive correlation between FEV1 and functional capacity through the assessment of the CKD children with age from 8 to 17 years. Children who performed better on the 6MWT had greater vital capacity and forced expiratory volume (FEV) values, demonstrating the influence of these respiratory measures on test outcomes. In contrast to ESRD, the change in functional capacity is consistent with change in MVV, FVC, FEV1, and PEF in normal healthy children which comes in accordance with research done by **Li *et al.*** [19] who measured the ventilatory functions (FEV1 and FVC) and functional capacity to healthy children aged between 7-16 years and the result showed significant association between FEV1 and 6MWT.

Also, another study done by **Camarri *et al.*** [20] found a significant association between FEV1 of ventilatory functions and the 6MWT.

CONCLUSION

Children with ESRD had a lower weight and height values and also ventilatory functions and functional capacity than normal children. Changes in the ventilatory functions led to changes in functional capacity in normal healthy children within different age groups that were large positively correlated. But in ESRD children, the positive correlations that were found within different age groups were not statistically significant.

Conflict of interest: None.
Financial disclosures: None.

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