Original Article

Assessment of Right Ventricular Myocardial Dysfunction in Children on Hemodialysis

Manal Abd Elsalam[1], Tagreed Abdelrahman[2], Ghada Mohamed S. Ahmad[2], Rasha M Goda[1], Nadia Youssef Riad[3], Taher Said[4]

1. Department of Pediatrics, Faculty of Medicine (for Girls), Al-Azhar University, Cairo, Egypt.
2. Department of Cardiology, Faculty of Medicine (for Girls), Al-Azhar University, Cairo, Egypt.
3. Department of Clinical Pathology, National Heart Institute, Cairo, Egypt.
4. Islamic Center of Cardiology, Al-Azhar University, Cairo, Egypt.

ABSTRACT

Introduction

Little attention has been paid to evaluating the right ventricle (RV), considered the forgotten side of the heart. Adenine DiMethyl Arginine (ADMA), growth differentiation factor15 (GDF-15), and highly sensitive (hs-CRP) may play a role in the development of RV dysfunction.

Aim of the Study: To reveal right ventricular (RV) function via conventional echocardiography and the new echocardiography (ECHO) modality to reveal the long-term impacts of hemodialysis (HD)on the RV in children on HD patients and assess the relationship between RV dysfunction and (ADMA), (GDF-15) and hs-CRP.

Methods: (ADMA, GDF-15, and hs-CRP) were analyzed in forty pediatric patients on HD and their forty controls. Also, the right ventricle was assessed by conventional Echo Doppler modalities, tissue Doppler imaging (TDI), and global RV strain by speckled tracking ECHO in the same line with routine laboratory investigations.

Results Significantly higher levels of ADMA, GDF-15, and hs-CRP in HD children than controls. Reduced RV function was detected in 16 (40%) out of 40 children. Significantly lower RV ventricular functions – RV Ejection Fraction & RV Fractional area change (RVEF % and RVFAC) and higher TV A vel, and TV E A vel ratio were found in (HD) group than in controls. Significant decrease in TDI tricuspid annular velocities E′) with significantly decreased right ventricular strain detected by TDI as well as STE in hemodialysis children than in their controls.

Conclusion: RV dysfunction is not uncommon in HD children; 2D-FAC is a traditional ECHO parameter for detecting right ventricular dysfunction in HD children; moreover, STE-GLS of the RV is an easily feasible assessment method, especially in those patients. ADMA is highly sensitive in predicting RV dysfunction in HD children.

Keywords: Right ventricle, ECHO, hemodialysis, children, ADMA, (GDF-15).

Corresponding Author : **Manal Abdel Salam,MD.**
Department of Pediatrics, Faculty of Medicine (for Girls), Al-Azhar University, Cairo, Egypt.
Email : Manal24969@gmail.com
Tel : 01006337676

INTRODUCTION

Cardiovascular risk is common, particularly with patients with end-stage renal disease on hemodialysis. Cardiac insufficiency due to uremia is, therefore, mainly due to non-specific pathological changes rather than pure renal insufficiency. Many studies have shown that the risk of adverse cardiovascular events is significantly increased and persistent in all patients treated with HD, especially those who have just started HD treatment **[1].**

The pathogenesis of CVD in hemodialysis patients is multifactorial, being related to traditional, known cardiovascular factors but also uremia-specific processes (e.g., uremia, alterations in phosphate and calcium metabolism, severe anemia, arterial remodeling, and hemodynamic overload) **[2].** Patients with end-stage renal disease have elevated levels of cardiac biomarkers, despite no apparent signs of cardiac dysfunction or radial damage; this is related to CKD comorbidities and reduced renal clearance per se **[3, 4]**.

Traditional echocardiography may not be capable enough to detect early cardiac abnormalities in CKD patients **[5].** There are no investigations of that concern to detect diagnostic tools to evaluate the right ventricular (RV) functionality in children on hemodialysis. In a comprehensive literature survey, no published study on pediatric patients addresses this issue.

In addition, only a few studies explore the importance of cardiac biomarkers in pediatric CKD patients **[6–9].** Analyzing cardiac biomarkers and traditional and new ECHO modalities in children with CKD on maintenance hemodialysis may improve diagnostic accuracy and facilitate the prediction of CVD, mainly the RV, which may improve clinical outcomes. Therefore, the current study contributes new, valuable evidence to fill the scientific gap in assessing right ventricular dysfunction.

METHODS

This is a case-control study conducted during the period from December 2021 to April 2022; it included 40 children recruited from the Pediatric Nephrology & Hemodialysis Unit, Al-Zahraa University Hospital (Cairo, Egypt); these are the patient's numbers who attended the pediatric hemodialysis unit during the period of the study; they were dialyzed three times per week for 4 hours/setting with low flux polysulphone dialyzer on Fresenius 4008S Classic machine **[10].**

The patient's ages ranged between 4-18 years (23 males and 17 females), and another 40 healthy children in the control group (18 males and 22 females), the sample size is appropriate, the required sample is 36 cases **[11]**. Regarding the etiology of CKD in the patient's group, acquired causes were found in 40%, then hereditary in 22.5%, then congenital in 15%, followed by metabolic in 2.5%. Still no known cause was detected in 20% of the cases.

Written consent was obtained from the participating parents in adherence to the guidelines of the ethical committee of AL-Zahraa University Hospital, Al Azhar University Faculty of Medicine (for Girls), Cairo, Egypt. This study was conducted with the participation of the

internal clinic's pediatric (nephrology and hemodialysis), clinical pathology, and cardiology departments. Children with structural heart diseases were excluded from the study. All study populations were subjected to entire history taking, including etiology, the onset of CKD, duration of hemodialysis, cardiac symptoms, medications, addition to routine and specific laboratory investigations and radiological investigation that assess the right ventricular function by traditional tissue doppler imaging and Speckle Tracking Echocardiography.

Laboratory investigations Sampling

- Blood samples were obtained (before starting a dialysis session in the morning after an overnight fast of at least 12 h. Blood was withdrawn using a vacuum system into three tubes; one containing EDTA and two gel vacuum tubes. A sample of EDTA was used to analyze CBC on the automated cell counter Swelab alpha. Another gel tube was used to measure urea, creatinine, calcium, phosphorous, potassium, cholesterol, and triglycerides.
- The third tube was centrifuged, & serum was separated into three boxes, carefully labeled, & stored at -20^{0}C until the assay of hsCRP, ADMA, & GDF15 by ELISA using the kits supplied by NOVA; Bioneovan Co., Ltd.
- Assay range of hsCRP: 0.3ng/ml -10 ng/ml **[12].**
- Assay range of ADMA: 2ng/ml - 150ng/ml **[13].**
- Detection range of GDF-15:15.6 pg/ml -1000pg/ml. www.bt-laboratory.com

Radiological investigation

ECHO Assessment

- Trans-thoracic echocardiography (TTE) evaluation was performed in the Cardiology department using Vivid-7 GE system (GE Ultrasound; Horten, Norway) with tissue Doppler imaging capability. Cases were examined by multi-frequency (2.5 MHz) matrix probe M3S. 2D Guided M-Mode, 2D, Conventional Doppler (pulsed and continuous wave), and color flow mapping in the standard views from all accessible windows were obtained with ECG physio signal displayed with all detected echo-Doppler studies. The same investigator made all measurements over at least three cardiac cycles, and the average value for each parameter was calculated.
- To avoid the effect of volume overload, echocardiography was done within 1-2 hours after dialysis when patients' weight was close to their target one. All parameters were taken based on the American Society of Echocardiography standards **[14].**
- Although all patients received a comprehensive evaluation of the size and function of all cardiac chambers, the current study reports only those concerning the RV systolic function and mechanics. Four-chamber view focused on the RV (with the patient in left lateral decubitus position) to calculate distinct indicators of RV size and function, and then the offline analysis of the recorded images was done e using a computer.
- **Assessment of right ventricular systolic functions:**

1- M-mode assessment for measuring tricuspid annulus plane systolic excursion (TAPSE): Right ventricular function is often assessed by measuring the upper-caudal excursion capability of the tricuspid valve annulus during ventricular systole by measuring (TAPSE). A value of less than 10mm is consistent with RV systolic dysfunction.TAPSE is defined by the distance of systolic excursion of the RV annular segment along its longitudinal plane from a standard apical 4-chamber window TAPSE index can be quickly evaluated on M-mode echocardiography **[15].**

2- 2D evaluation of RV dimensions, volumes & fractional area change (FAC) :

Using 2D echo modality by tracing the endocardial border, we obtain the following measures:

a- RV basal diameter, RV mid diameter, and RV longitudinal diameter.

b- RV end diastolic and end systolic volumes from which RVEF is automatically calculated by the echo machine.

c- Fractional area change (FAC) is defined as (end-diastolic area − end-systolic area) / end-diastolic area × 100.

FAC is another parameter that offers a good perception of global RV systolic function; if the tracing is carefully done to include the apex, free wall, or trabeculae in the RV chamber, a value of less than 35% implies RV systolic decay **[16].**

3- Conventional Doppler evaluation of tricuspid flow velocities for assessment of RV diastolic function:

Using pulsed wave Doppler the following velocities were assessed: TV early diastolic velocity (TV E vel.) TV late diastolic velocity (TV A vel.) and E/A ratio.

4- Tissue Doppler Imaging (TDI) for measuring tricuspid annular velocities and RV strain:

- Pulsed wave tricuspid annular peak systolic velocity (S), early (E'), and late (A) peak annular diastolic velocities were recorded.
- RV global TDI strain was evaluated using average measures of free wall and septal wall TDI strain of the RV.

5-Assessment of RV Global Longitudinal Strain using 2-D Speckle Tracking Echocardiography:

- Using a 2D greyscale image of a modified apical four-chamber view to proper visualization of the RV where the endocardial boundary was manually traced and automatically modified to accommodate the whole myocardium. The grayscale frame rate was kept between 60-90 frames/s; a minimum of three cardiac cycles were obtained for each loop. To guarantee appropriate tracking, the thickness of the myocardium was manually adjusted to the area of interest **[17].**
- All images were stored in a cine-loop format, and data were transferred to the workstation for further offline analysis of RV-GLS using the EchoPAC software version 110-1.3 for GE.E9 **[18].**

STATISTICS

Data were collected, revised, coded, and entered into the Statistical Package for the Social Science version 21(IBM Corp., Armonk, NY, USA).

- Spearman correlation coefficients were used to assess the correlation between two studied parameters in the same group.
- The receiver operating characteristic (ROC) curve estimated the best cutoff point with sensitivity and specificity.
- Interpretation of probability values was as follows: P >0.05 as nonsignificant, P <0.05 as significant.

RESULTS

Regarding clinical and laboratory data:

There was a significant increase in systolic blood pressure and serum (urea, creatinine, phosphate, cholesterol, triglyceride, and potassium in the patients-group compared to controls with no significant difference in the serum calcium level. There was also a more substantial increase in serum ADMA, GDF-15, and hsCRP in the patient's group than in their controls, as seen in **(Table 1).**

Regarding RV function:

The main objective of the current study is to evaluate RV function and the best diagnostic tool for assessment; Children on hemodialysis show significantly decreased 2D-RVFAC and 2D-RVEF than their controls. Meanwhile, in hemodialysis children, there is a significant increase in TV A vel and a decrease in TV E/A ratio than their controls; in addition, Tricuspid annular velocities show a considerable reduction in average E vel. with significant TDI RV strain in patients than their controls. Also, a substantial decrease in RV strain was detected by 2D- STE GLS in the hemodialysis group, as shown in **(Table 2), (Figure 1, 2, 3).**

On evaluating the prevalence of RV dysfunction in children on hemodialysis, 16 patients (40%) out of 40 patients had impaired RV function, as shown **in (Table 3).**

Correlations between laboratory markers and RV function Echo parameters:

ADMA, GDF15, and hsCRP negatively correlated with 2D-RVFAC, TV A vel. , ADMA, and hsCRP are negatively correlated with TDI average S. Meanwhile, ADMA is solely negatively correlated with TDI average E T. Annular as shown in **(Table 4).**

ROC curve analysis of the study biomarkers it revealed ADMA is a highly sensitive marker for RV dysfunction that based on FAC with a sensitivity of 93.8% and a specificity of 73%; meanwhile, hs-CRP showed a sensitivity and specificity of 81.3 and 73%, respectively, but GDF-15 had low sensitivity and specificity for the detection of RV dysfunction at 68.8 % and 60%, respectively, as shown in **(Table 5)** and **(Figure 4).**

Table 1: Comparison between patients and the control group regarding anthropometric measurements, blood pressure, and laboratory data

Groups	Control group	Patients group	Mann Whitney test	
Variables	**No. = 40**	**No. = 40**	**t**	**P-value**
Age (years)	10.83 ± 4.19	11.95 ± 3.37	-1.313•	0.193
z-Wt	0.17 (-0.52 – 0.74)	-0.49 (-0.74 – 0.14)	-2.368	**0.018**
z-Ht	0.52 (-0.39 – 1.05)	-0.13 (-0.91 – 0.39)	-2.893	**0.004**
z-BMI	0.01 (-0.54 – 0.35)	-0.25 (-0.63 – 0.23)	-1.179	0.238
z- Systolic blood pressure IQR	-0.8 (-1.15 – (- 0.34)	0.74 (0.20-1.28)	7.435	**0.001**
z-Ddiastolic blood pressure)	-0.92 (-092- (-0.55)	0.55 (0.55-1.29)	-7.464	**0.001**
Urea (mg/dl)	24.75 ± 7.07	161.15 ± 67.13	-12.781•	**0.001**
Creat (mg/dl)	0.64 ± 0.17	2.96±1.87	-7.806•	**0.001**
Ca (mg/dl)	10.14 ± 0.76	10.03±1.91	0.361•	0.719
Phos (mg/dl)	3.96 ± 0.34	5.85±1.19	-9.626•	0.001
K (mEq/l)	3.96±1.04	4.42 ± 0.46	2.552•	**0.013**
Cholesterol (mg/dl)	116.68 ± 10.88	135.9±25.5	-4.386•	**0.001**
TG(mg/dl)	120.15 ± 10.75	136.75±13.82	-5.998•	**0.001**
Median (IQR) ADMA (ng/ml)	25 (20-30)	72.5(55-93.7)	-7.227	0.001
Median (IQR) GFD-15 (pg/ml)	130 (91.5-169)	650 (415.5-794.5)	-7.520	0.001
Median (IQR) hs-CRP (ng/ml)	4.05 (3.60-4.75)	13.05 (9.90-16.95)	-7.695	0.001

Table 2: Comparisons between the controls and patients group regarding RV parameters by conventional Echo Doppler and STE

Variables / Groups		Control group No. (40)	Patients group No. (40)	Independent t-test	
		Mean ± SD	**Mean ± SD**	**t**	**P-value**
RV Basal Diameter		30.0 ± 8.0	29.5±8.9	-.293	0.770
RV Mid Diameter		26.9 ± 9.2	27±9.1	.066	0.947
RV Longitudinal Diameter		47.6 ± 14.2	52.4 ±15.0	1.862•	**0.05***
2D-RVEDV		25.2 ± 13.1	27.2 ±14.8	.557	0.579
2D-RVESV		10.6 ± 2.9	12.5 ±7.3	.952	0.344
2D-RVFAC		50.05 ± 12.5	40.9 ±15.5	-3.245•	**0.002***
2D-RVEF		59.5 ± 15.3	52.5 ±12.	-2.433 •	**0.017***
TAPSE		19.0 ± 4.9	17.5 ±5.6	-1.263	0.210
TV E vel.		0.53 ± 0.2	0.56 ± **0**.18	.557	0.579
TV A vel.		0.42 ± 0.1	0.6 ±**0**.24	5.475•	**0.001***
TV E/A ratio		1.2 ± 0.4	0.9 ±**0**.46	-3.363•	**0.001***
Average TDI tricuspid annular velocities	**Average S**	7.4 2.3	6.8± 2.4	77	.077
	Average E	10.1 3.1	6.7± 2.7	51.96•	**0.001**
Average TDI RV strain		26.5 7.5	18.2± 8.3	50.6•	**0.005**
RV 2D-STE-GLS		24.0± 5.4	17.2± 4.1	76.3•	**0.001**

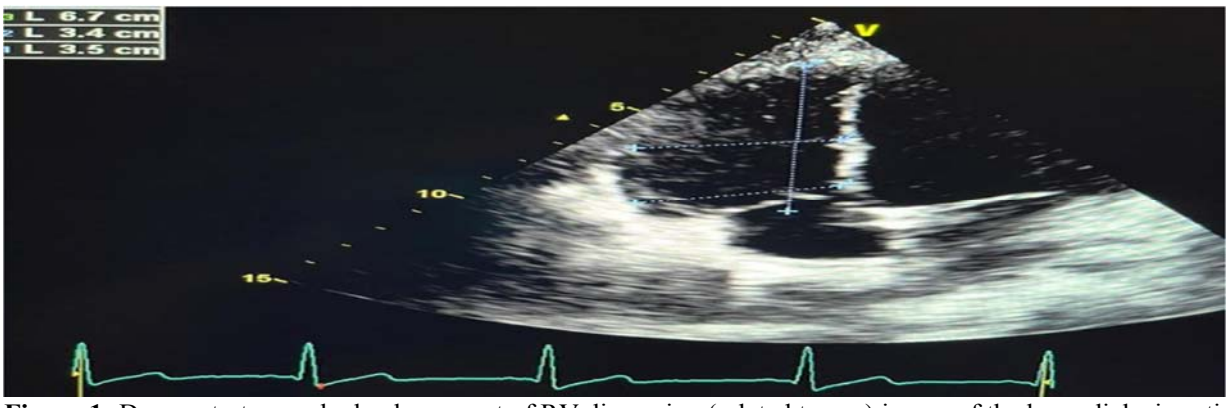

Figure 1: Demonstrates marked enlargement of RV dimension (related to age) in one of the hemodialysis patients.

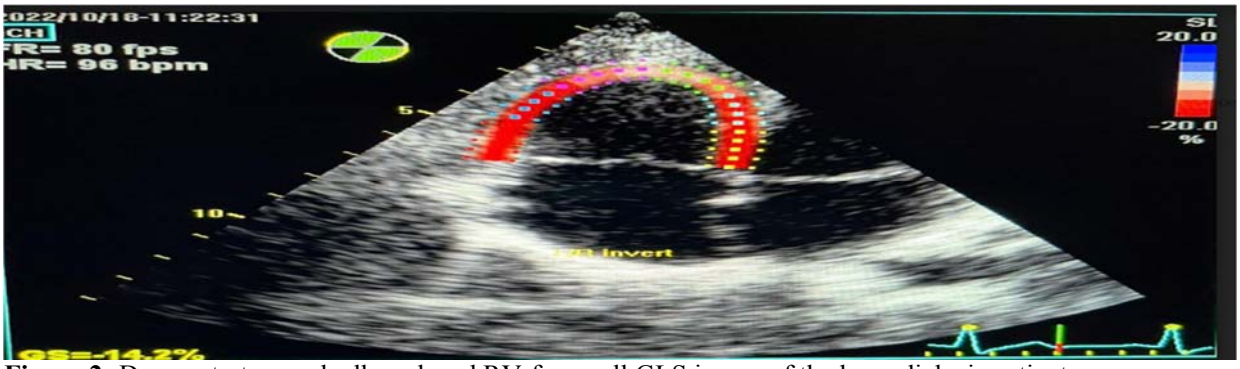

Figure 2: Demonstrates markedly reduced RV-free wall GLS in one of the hemodialysis patients.

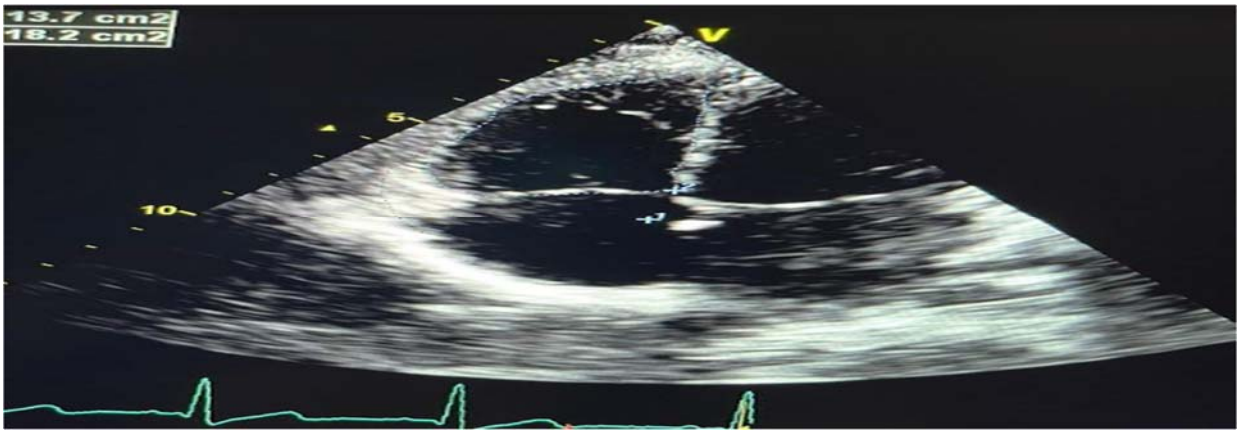

Figure 3: Demonstrates markedly reduced FAC in one of the hemodialysis patients.

Table 3: The incidence of RV Dysfunction in the hemodialyzed group vs. the control group.

Total cases (40)		No.	%
RV function status	Normal	24	60.0%
	Impaired	16	40.0%

Table 4: Correlation between GDF-15, ADMA, and hsCRP with RV parameters by conventional Echo Doppler and STE.

Variables		GDF-15		ADMA		Hs CRP	
		r	P-value	r	P-value	r	P-value
RV Basal Diameter		-0.080	0.488	0.097	.398	-0.054	0.640
RV Mid Diameter		-0.023	0.838	-0.018	0.875	0.002	0.986
RV Longitudinal Diameter		0.127	0.267	0.163	.154	0.079	0.492
2D-RVEDV		0.086	0.453	0.025	.830	-0.070	0.544
2D-RVESV		0.131	0.253	0.067	.558	0.041	0.724
2D-RVFAC		-0.251	0.027	-0.277	.014	-0.308	**0.006**
2D-RVEF		-0.136	0.235	-0.238	.036	-0.295	**0.009**
TAPSE		-0.110	0.336	-0.148	.192	-0.109	0.337
TV E vel.		0.101	0.375	0.015	.894	-0.011	0.922
TV A vel.		0.389	0.001	0.335	.003	0.253	0.025
TV E/A ratio		-0.275	0.014	-0.259	0.021	-0.351	**0.002**
Average TDI T. Annular velocities	**Average S**	-0.055	0.074	-0.240	0.033	-0.368	0.021
	Average E	0.232	0.155	-0.376	**0.001**	0.291	0.073
Average TDI RV strain		-0.376	**0.001**	-0.383	**0.001**	-0.431	**0.001**
STE RV GLS		-0.523	**0.001**	-0.497	**0.001**	-0.501	**0.001**

Table 5: The Cut-off point, sensitivity, and specificity of ADMA, hs CRP, and GDF-15 as predictors of RV dysfunction in children on hemodialysis

Variables	Cut off point	AUC	Sensitivity %	Specificity %
ADMA ng/ml	> 52.5	0.852	93.8	73
Hs CRP ng/ml	> 980	0.779	81.3	73
GFD-15(pg/ml)	> 415	0.81	68.8	62.8

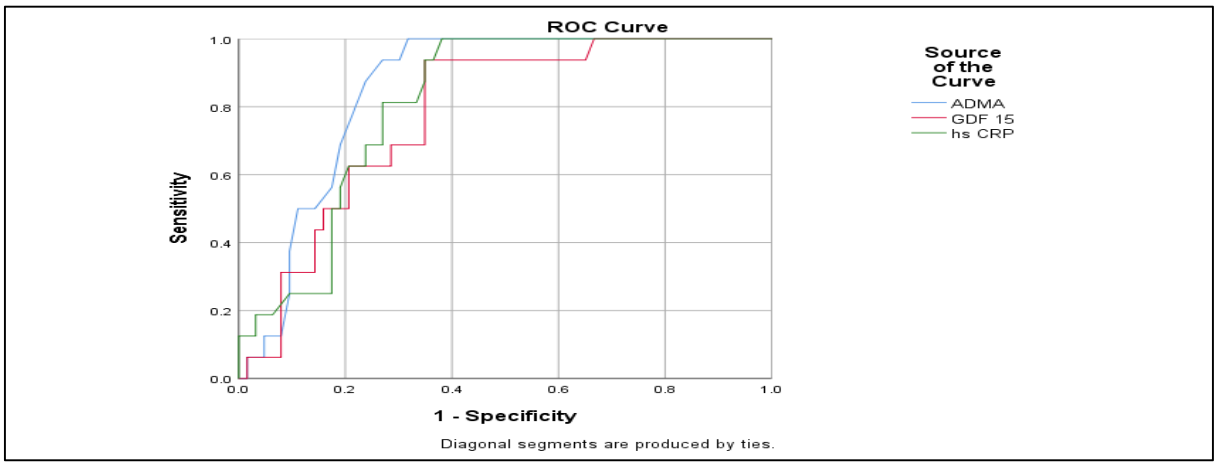

Figure 4: ROC curve for sensitivity and specificity of ADMA, hs CRP, and GDF-15 in detecting RV dysfunction.

DISCUSSION

Most of the published studies are concerned with LV assessment in hemodialysis children. The current study analyzed the right ventricular performance in those patients. RV function was judged by conventional echocardiographic methods and by the recent echo modality 2D-STE; in addition, it detected its associations with hs CRP, ADMA, and GDF15 concerning the structural and functional abnormalities of the right ventricle. In the current study results, 16 (40%) out of 40 cases were associated with RV dysfunction; this is a significant proportion among those cases, and the reasons and treatment must be sought.

Published reports concluded that RV dysfunction is a predictor of adverse outcomes in many heart diseases; however, there is a lack of data regarding the changes in RV geometry and function in pediatric patients on HD. RV systolic dysfunction was relatively common (27%) in HD patients and was a significant predictor of mortality [19], studied nondiabetic normotensive HD patients and found that both RV systolic and diastolic functions were reduced compared with healthy subjects [20].

In addition, [21-23] reported RV dysfunction is common in HD patients, but unfortunately, these findings are recorded in the adult population. Moreover, RVD could also affect LV filling via interventricular interaction [24]. Conversely, LV dysfunction did not significantly influence RV parameters [25].

Right ventricle dysfunction is a significant marker of poor prognosis, regardless the degree of left ventricular dysfunction [26]. Therefore, an accurate and effective method was required for the RV assessment. The complex shape of the RV, and the relatively large

element of trabeculations, make its function more challenging to be assessed as compared to the left ventricle (LV) when using echocardiography [27]. The current study revealed a significant decrease in RV FAC in the hemodialysis group that estimates the global RV systolic function [28].

RV dysfunction may result from arteriovenous fistula [29], which may share in LV dysfunction in dialysis patients, triggering LV dysfunction through right-to-left ventricular interdependence. Moreover, the hemodynamic changes in the internal environment in hemodialysis patients are complicated, including body-fluid fluctuation, electrolyte disorder, hyperparathyroidism, and uremic toxins [30]. These unfavorable factors lead to prolonged active contraction and increased oxygen consumption of cardiomyocytes, eventually causing LV and RV dysfunction [31].

We reported a significant increase in TV A vel m/s and a decrease in TV E/A ratio; in children on hemodialysis than in healthy controls that denote diastolic dysfunction in the hemodialysis group. These results are similar to the data published by other authors. Tamulėnaitė et al. reported in a case-control study that impaired right ventricular diastolic function might be explained by the presence of left ventricular overload and increased pressure on the right heart and intravascular volume [32]. Also, a study on ESRD patients reported a significant reduction in the E/A ratio in hemodialysis patients compared to controls [33].

dysfunction in comparison with GDF 15, and hs-CRP. In addition, other RVFAC and right ventricular ejection fraction (RVEF) can change with a change in load without any actual change in myocardial contractility and therefore do not reflect innate myocardial function [34].

In the current study, the TDI evaluation of the RV is not affected by loading conditions in those patients, revealing a significantly low early diastolic velocity (a) that represents the velocities of the myocardial wall movement during the rapid early filling of the ventricle without significant (s) changes. In addition, a significant reduction in global RV TDI strain is recorded in the HD group, consistent with [32]. Who reported similar findings in adult HD patients.

The present study demonstrated significantly reduced 2D- STE derived RV -GLS.in the hemodialysis group that denotes impaired RV deformation due to increased RV preload and filling pressure. A few articles adopted 2D-STE as a tool to appraise the right ventricular (RV) functionality in subjects with ESKD [35].

On [A5] assessing ADMA, GDF 15 and hsCRP as markers of RV dysfunction in children on HD, significantly increased their levels than the controls and negatively correlated with 2D-RVFAC, TV E/A ratio, and TDI RV strain.

Moreover, these markers had a strong negative correlation with 2-D STE-derived RV GLS; in light of such evidence, it can be postulated that the serum ADMA, GDF 15, and hs-CRP levels may be associated with (RV) dysfunction, but ADMA is a highly sensitive and specific marker for RV studies reported ADMA association with LV dysfunction [36-37]. To the

best of our knowledge, the current study is the first report concerned with the association of the present study markers with RV dysfunction.

GDF15 level is increased during CVD development and progression and can prognosticate disease progression, but it cannot be used as a reliable diagnostic test for routine clinical use [38]. Regarding hs-CRP, many studies concerned and detecting the association as a marker of left ventricular dysfunction [39].

In the current study, although RV FAC, TAPSE, and RVEF are traditional echocardiographic tools used for the assessment of RV function, the use of the up-to-date STE modality can detect the subtle change in RV function even before the development of overt geometric and structural abnormalities of the RV in those population, being its angle independent and not affected by loading conditions, further research is recommended in the future.

CONCLUSIONS

RV dysfunction is not uncommon in HD children. There is a significant RV systolic and diastolic dysfunction with no substantial change in RV structure. In addition, there was a significant association between ADMA, GDF 15, and hs-CRP and RV dysfunction; but ADMA is the most sensitive and specific indicator for it. RV assessment could be a part of routine ECHO in children on hemodialysis.

ABBREVIATIONS

ADMA	Adenine DiMethyl Arginine	RV	Right Ventricle
CKD	Chronic Kidney Disease	RVEF	RV Ejection Fraction
CVD	Cardiovascular Disease	RVFAC	RV Fractional area change Tricuspid
ECHO	Echocardiography	TAPSE	anomalies plane systolic excussions
EDTA	Ethylenediaminetetraacetic acid	TDI	Tissue Doppler Imaging
FAC	Fractional area change	TTE	Transthoracic Echocardiography
GDF-15	growth differentiation factor15	TV E vel	TV early diastolic velocity
HD	Hemodialysis	TV A vel	TV late diastolic velocity
hsCRP	High sensitivity C reactive protein		

REFERENCES

1. Wang Y and Gao L): Inflammation and Cardiovascular Disease Associated With Hemodialysis for End-Stage Renal Disease. Front. Pharmacol., 2022 Feb.10; 13:800950. https://doi.org/10.3389/fphar.2022.800950
2. Tonelli, M.; Karumanchi, S.A.; Thadhani, R. Epidemiology, and Mechanisms of Uremia-Related Cardiovascular Disease. Circulation 2016; 133, 518–536.
3. Chesnaye NC, Szummer K, Bárány P, Heimbürger O, Magin H, Almquist T, Uhlin F, Dekker FW, Wanner C, Jager KJ, Evans M: Association between renal function and troponin T over time in stable chronic kidney disease patients. J Am Heart Assoc 2019; 8:e013091.
4. Song HL, Yang TT, Li GX: Assessing the cardiac function of patients with chronic kidney disease using N-terminal pro-brain natriuretic peptide precursor (NT-proBNP). Sichuan Da Xue Xue Bao Yi Xue Ban 2017; 48:561–565.
5. Edwards, N.C.; Hirth, A.; Ferro, C.J.; Townend, J.N.; Steeds, R.P. Subclinical abnormalities of left ventricular myocardial deformation in early-stage chronic kidney disease: The precursor of uremic cardiomyopathy? J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc. Echocardiogr. 2008; 21, 1293–1298.

6. Nalcacioglu H, Ozkaya O, Kafali HC, Tekcan D, Avci B, Baysal K: Is N-terminal pro-brain natriuretic peptide a reliable marker for body fluid status in children with chronic kidney disease? Arch Med Sci 2020; 16:802–810 18.

7. Karadaş U, Karadaş N, Bak M, Serdaroğlu E, Yılmazer MM, Meşe T: The role of cardiac troponin T in the detection of cardiac damage and long-term mortality in children with chronic renal disease. Turk J Pediatr 2019; 61:873–878 17.

8. Lipshultz SE, Somers MJ, Lipsitz SR, Colan SD, Jabs K, Rifai N: Serum cardiac troponin and subclinical cardiac status in pediatric chronic renal failure. Pediatrics 2003; 112:79–86 19.

9. Rinat C, Becker-Cohen R, Nir A, Feinstein S, Algur N, Ben-Shalom E, Farber B, Frishberg Y: B-type natriuretic peptides are reliable markers of cardiac strain in CKD pediatric patients. Pediatr Nephrol 2012; 27:617–625.

10. Krejcie R.V., Morgan D.W. Determining Sample Size for Research Activities. *Educational and Psychological Measurement.* (1970).

11. KDIGO: Clinical Practice Guideline for Anemia in chronic kidney disease, Kidney Int Suppl; 2017; 2: 283–287.

12. Mercuri A, Turchi S, Borghini A, Chiesa MR, Lazzerini G, et al.,: Nitrogen biobank for cardiovascular research. Curr Cardiol Rev; 2013; 9(3):253–9.

13. Kielstein J, Impraim B, Simmel S, Bode-Boger S, Tsi-kas D, et al., Cardiovascular effects of systemic nitric oxide synthase inhibition with asymmetrical dimethylarginine in humans. Circulation; 2004; 109: 172–7.

14. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, et al.: Recommendations for evaluating left ventricular diastolic function by echocardiography. Eur J. Echocardiogr; 2009; 10:165–193.

15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, et al.: Recommendations for chamber quantification. Eur J Echocardiogr; 2006; 7(2) 79- 108.

16. Lang, R.M.; Badano, L.P.; Mor-Avi, V.; Afilalo, J.; Armstrong, A.; Ernande, L.; Flachskampf, F.A.; Foster, E.; Goldstein, S.A.; Kuznetsova, T.; et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J. Am. Soc. Echocardiogr. Off. Publ. Am. Soc. Echocardiogr. 2015; 28, 1–39.

17. Mahmoud M, Shalan IM and Azeem HA. Impact of pulmonary hypertension on biventricular functions tissue doppler echocardiographic study. Egyptian Journal of Chest Diseases and Tuberculosis. 2017; 66(1):137-44.

18. Silverton NA, Lee JP, Morrissey CK, et al. A comparison of left-and right-sided strain software for the assessment of intraoperative right ventricular function. Journal of cardiothoracic and vascular anesthesia. 2019; 33(6):1507-15.

19. Karavelio ˘glu, Y.; Özkurt, S.; Kalçik, M.; Karapinar, H.; Arisoy, A. Echocardiographic assessment of right ventricular functions in nondiabetic normotensive hemodialysis patients. Interv. Med. Appl. Sci. 2015; 7, 95–101.

20. McMahon, L.P.; Roger, S.D.; Levin, A. Development, prevention, and potential reversal of left ventricular hypertrophy in chronic kidney disease. J. Am. Soc. Nephrol. 2004; 15, 1640–1647.

21. Beigi AA, Sadeghi AM, Khosravi AR, et al. Effects of the arteriovenous fistula on pulmonary artery pressure and cardiac output in patients with chronic renal failure. J Vasc Access. 2009; 10:160–166.

22. Alhamad EH, Al-Ghonaim M, Alfaleh HF, et al. Pulmonary hypertension in end-stage renal disease and post renal transplantation patients. J Thorac Dis. 2014; 6:606–616.

23. Yigla M, Banderski R, Azzam ZS, et al. Arterio-venous access in end-stage renal disease patients and pulmonary hypertension. Ther Adv Respir Dis. 2008; 2:49–53.

24. Piazza G, Goldhaber SZ. The acutely decompensated right ventricle: pathways for diagnosis and management. Chest. 2005; 128:1836–1852.

25. Paneni, F.; Gregori, M.; Ciavarella, G.M.; Sciarretta, S.; Palano, F.; Pignatelli, G.; Castello, L.; Domenici, A.; Punzo, G.; Tocci, G.; et al. Relation between right and left ventricular function in patients undergoing chronic dialysis. J. Cardiovasc. Med. (Hagerstown Md.) 2013; 14, 289–295.

26. Monitillo F1 , Di Terlizzi V , Ilaria Gioia M 3 , Barone R 2 , Grande D , Parisi G , Natale Daniele Brunetti ND 2 and Iacoviello M. J. Cardiovasc. Dev. Dis. 2020; 7, 12.

27. Moledina S, Pandya B, Bartsota M, Mortensen KH, McMillan M, Quyam S, et al. Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. Circ Cardiovasc Imaging. 2013; 6:407–14.

28. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23:685-713.

29. Kawut SM, Horn EM, Berekashvili KK, Garofano RP, Goldsmith RL, Widlitz AC, et al. New predictors of outcome in idiopathic pulmonary arterial hypertension. Am J Cardiol. 2005; 95:199–203.

30. London G. Pathophysiology of cardiovascular damage in the early renal population. Nephrol. Dial. Transplant. 2001; 16 (Suppl. 2):3–6.

31. Rudhani, I.D., Bajraktari, G., Kryziu, E., Zylfiu, B., Sadiku, S., Elezi, Y., Rexhepaj,

39. Silva D, de Lacerda A P: High-sensitivity C-reactive protein as a risk biomarker in coronary artery disease Rev Port Cardiol. 2012; 31(11):733-745.

N., Vitia, A., Emini, M., Abazi, M., Berbatovci-Ukimeraj, M., Kryeziu, K., Hsanagjekaj, V., Korca, H. and Ukimeri, A.: Left and Right Ventricular Diastolic Function in Hemodialysis Patients. Saudi Journal of Kidney Diseases and Transplantation, 2010; 21, 1053- 1057.

32. Tamulėnaitė E, Zvirblyte R, Ereminiene R, et al. Changes of left and right ventricle mechanics and function in patients with end-stage renal disease undergoing hemodialysis. Medicine. 2018; 54(5):87.

33. London, G.M., Marchais, S.J., Guerin, A.P., et al. Cardiac Hypertrophy and Arterial Alteration in End-Stage Renal Disease: Hemodynamic Factors. Kidney International.1993; 41, S42-S49.

34. Dandel M, Hetzer R. Echocardiographic assessment of the right ventricle: impact of the distinctly load dependency of its size, geometry, and performance. Int J Cardiol. 2016; 221:1132–1142

35. Jategaonkar SR, Scholtz W, Butz T, Bogunovic N, Faber L, Horstkotte D: Two-dimensional strain and strain rate imaging of the right ventricle in adult patients before and after percutaneous closure of atrial septal defects. Eur J Echocardiogr 2009; 10:499–502.

36. Unger E.D., Dubin R.F., Deo R., Daruwalla V., Friedman J.L., Medina C., Beussink L., Freed B.H., Shah S.J. Association of chronic kidney disease with abnormal cardiac mechanics and adverse outcomes in patients with heart failure and preserved ejection fraction. Eur. J. Heart Fail. 2016; 18:103–112.

37. Zhao JR, Zhang DY, Sun DZ. Correlation research on ADMA plasma levels and left ventricular function of peritoneal dialysis patients. Int J Clin Exp Med 2014; 7:4455–4460.

38. Wollert KC, Kempf T, Wallentin L. Growth differentiation factor 15 as a biomarker in cardiovascular disease. Clin

AUTHORS'´CONTRIBUTIONS

All authors have read and approved the manuscript.

Study conception and design: 1st & 2nd author.

Data acquisition: 3rd & 4th author.

Analysis and data interpretation: 3rd & 4th author.
Drafting of the manuscript: 1st author & 4th author.
Critical revision: 1st author.

STATEMENTS

Ethics approval and consent to participate

The local ethical committee permitted the study under the Helsinki declaration of Bioethics and its later amendments.
Informed consent (written form) was obtained from all participants or their caregivers.

Consent for publication

The attached manuscript, its contents, and materials have not been previously reported at any length or are being considered for publishing elsewhere.

Availability of data

The authors have indicated that the data and material are factual and genuine.

Author contributions

All authors listed approved paper publications..

Conflict of interest

No conflict of interest

Funding

No external fund

Submission Date: 23 /09/2022
Acceptance Date: 17/12/2022
Publication Date: 30/12/2022