Cardiac Biomarkers and Cardiovascular Outcome in Children with Chronic Kidney Disease

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Keywords. chronic kidney disease, echocardiography, H-FABP, PAPP-A, left ventricular mass.

Introduction. Myocardial dysfunction is a leading cause of mortality in chronic kidney disease (CKD) children specially those on regular hemodialysis. Cardiac biomarkers play a key role for early detection of myocardial injury. We aim to clarify the prognostic role of circulating cardiac biomarkers, heart type fatty acid binding protein (H-FABP) and pregnancy associated plasma protein-A (PAPP-A) in CKD children on regular hemodialysis.

Materials and Methods. This is a prospective case control study over 2 years duration. Initial assessment included 20 CKD children on regular hemodialysis and 20 age- and sex- matched healthy children as a control group. Serum level of H-FABP and PAPP-A were measured and correlated to conventional echocardiographic findings and cardiovascular outcome in CKD children.

Results. 60% of CKD children developed cardiovascular comorbidities. H-FABP and PAPP-A levels were significantly elevated especially in those with worse cardiovascular outcome. H-FABP and PASP-A levels were positively correlated with LVM index. At cut off point > 17.65 pg/mL, H-FABP has 91% sensitivity and 87.5% specificity for prediction of cardiac morbidity. Elevated H-FABP (OR = 33; CI 95%: 2.455 - 443.591), LVM indexed to body surface area (OR = 21; CI 95%: 1.777 - 248.103), LVM indexed to lean body mass (OR = 15; CI 95%: 1.652 -136.172), elevated PAPP-A (OR = 9.8; CI 95%: 0.898 - 106.845) and Hypertension (OR = 8.333; CI 95%: 1.034 - 67.142) are the main risk factors for cardiac morbidities in CKD children.

Conclusions. Elevated H-FABP and PAPP-A are valuable prognostic markers for cardiovascular outcome in CKD children on regular hemodialysis.

IJKD 2019;13:120-8
www.ijkd.org

Original Paper

INTRODUCTION

The long-term survival of children with advanced chronic kidney disease (CKD) remains low compared to general population, specifically, those on regular hemodialysis. Even in developed countries, the life span of CKD children is shortened by 40-60 years than healthy peers.[1] In spite of several advances in dialysis therapies, the mortality of patients with end-stage renal disease is 30 folds higher than that of age and ethnic matched healthy individuals. Cardiovascular complications and death account for 40% and 20%, respectively, of all morbidity and mortality in children on chronic dialysis.[2]

The American Heart Association enrolled

pediatric CKD in the highest risk category for the development of cardiovascular disease.[3]

Myocardial dysfunction starts early in the course of CKD in children and progresses rapidly as renal function declines, especially in those on regular hemodialysis. Therefore, it is considered as a serious complication of CKD that can significantly affects patient survival, impairs their quality of life and substantially increases health care costs. Cardiac dysfunction is a multifactorial, progressive process that requires early diagnosis and intervention.[4]

Left ventricular mass (LVM) have been considered as a predictor of cardiovascular morbidity and mortality in many clinical disorders including CKD. Cardiac magnetic resonance is the best method for measuring LV mass. However, in routine practice, echocardiography remains the preferred method due to its good accuracy, low cost, and wide accessibility.[5] LVM varies with age during child growth so indexing LVM for anthropometry is mandatory.[6]

As echocardiography needs experience and there is observer variability, using cardiac biomarkers have been emerged as quantitative methods for assessment of myocardial performance for early detection and follow up of myocardial dysfunction.[7]

Pregnancy associated plasma protein-A (PAPP-A) is a high-molecular-weight zinc-binding metalloproteinase. It cleaves inhibitory insulin-like growth factor binding protein 4 (IGFBP-4) which is a major regulator of local insulin growth factor (IGF) action. Its elevated level has been emerged as a promising biomarker for cardiovascular risk stratification even in troponin- negative individuals.[8]

Heart type fatty acid binding protein (H-FABP) is a low molecular weight (15 kDa) protein that accounts for 5-15% of the cardiomyocytes cytosolic proteins. H-FABP is a cytoplasmic protein that isn't found outside the cell or in plasma under normal conditions. It is released rapidly into the blood following myocardial damage before the cell gets disrupted. Additionally, H-FABP can provide a dynamic view of the remodeling process.[9]

In spite of the promising role of PAPP-A and H-FABP for detection of cardiac impairment in adult patients, there is little information on the value of these cardiac markers in children. Additionally, the prognostic value of these myocardial damage markers has not yet been elucidated in patients with CKD. The current study aims to explore the role of cardiac biomarkers: PAPP-A and H-FABP for early detection of myocardial dysfunction in children with CKD and to clarify the prognostic value of these biomarkers to prevent progression of CVD in such patients in comparison with conventional echocarioography.

MATERIALS AND METHODS

Study Design

This was a hospital-based prospective case control study conducted at Al–Zahraa university hospital, Cairo, Egypt.

Ethical Consideration

The study was performed in accordance with the local ethics committee of Al-Azhar university, Cairo, Egypt. Informed written consent was taken from the parents and personal information was kept confidential. Prior to enrollment, the purpose of the study was explained to parents.

Study Population

Case Group. In this group included 20 children with CKD on regular hemodialysis for at least 6 months. Children aged 5-15 years with CKD who attended hemodialysis at pediatric nephrology ward of Al–Zahraa university hospital from February 2015 to February 2017 were enrolled in the study. Children with congenital, rheumatic heart disease, acute kidney injury and children with CKD who didn't require hemodialysis were excluded from the study.

Control Group. Included 20 age- and sex-matched healthy children who were selected randomly from outpatients pediatric clinic at Al–Zahraa university hospital. They did not have any acute or chronic systemic illness, renal or urinary disorders, congenital or acquired heart diseases, hypertension or obesity as confirmed by detailed history, examination and echocardiography.

Follow-up. After the initial assessment, patients were followed-up from February 2015 for 2 years. Echocardiographic assessment was done regularly every 6 months and urgent echocardiography was done when patients suffered from cardiovascular deterioration. All cardiovascular morbidity and/or mortality over these 2 years were recorded and confirmed by clinical manifestation and echocardiography at the time of admission showing marked reduction of ejection fraction and impaired

both systolic and diastolic function in comparison to their previous echocardiography.

Twelve out of the 20 CKD children developed congestive heart failure that needed hospital admission. Three of them died due to cardiovascular events.

Clinical History and Examination. All the studied children were subjected to a detailed history including socio demographic data, presenting symptoms, duration of renal impairment and dialysis, renal and cardiac symptoms, results of renal biopsy, and current medications.

Complete systemic and cardiac examinations were done at the time of initial evaluation. Physical growth was evaluated by measurement of weight and height of all included children and was expressed in terms of a Z-score relative to age and sex. Z-score was calculated as $Z = (\chi-\mu)/\sigma$ where χ is the observed measurement, μ is the expected measurement (population mean) and σ is the standard deviation of the population.[10] Body surface area (BSA) was detected by blotting the weight and length on the surface area nomogram.[11] Dry weight was used to avoid the effect of pre-dialysis salt and water retention.

Echo-Doppler Evaluation. Trans-thoracic M-mode, two dimensional (2D), and Doppler echocardiographic examination in standard views (parasternal long axis, parasternal short axis, apical four and two chamber views) from all accessible windows with loop recording of 2-3 cycles were performed for all patients and control subjects in both supine and left lateral position using VIVID 7 GE system. All cases were examined using multifrequency (2.5-3.5 MH) Matrix probe M3S with simultaneous electrocardiographic recording to allow timing of events. All parameters were evaluated according to the standards of the American Society of echocardiography.[12] To avoid false impact of volume overload on the heart; echocardiographic assessment was done just after the hemodialysis session.

The PASP was estimated from the tricuspid resurge (TR) signals that was present in all the study cases, using color flow guided CW Doppler and calculated as maximum systolic pressure gradient across the tricuspid valve + 10 mmHg as an assumed right atrial pressure.[12]

Early (E) and late (A) trans-mitral and trans-tricuspid flow velocities were measured by conventional pulsed wave Doppler then E/A ratio was calculated. Measurement of LVM was performed in the parasternal long-axis view. LVM was calculated using the following equation:[13]

LVM = 0.8 (1:04 [(LVED + posterior wall thickness + interventricularseptal thickness) 3 -LVED3)] + 0.6.

Relative wall thickness (RWT) was calculated[14] as (2 × PWd) / LVEDD.

LVM is continuously changeable with age and it is in direct proportion with the body size, hence adjustment of LVM to the body size should be done for proper accurate assessment of cardiovascular risk. Indexing LVM to body surface area (BSA) or to height or to estimated lean body mass (eLBM) are emerging normalization method in clinical practice**.** Indexing LVM/BSA was calculated by dividing LVM by BSA. Indexing LVM to height raised to an exponential power of 2.7 (LVM/height ($g/m^{2.7}$) was calculated by dividing LVM by height in meters to the power of 2.7.[15] LVH was defined as LVM/$height^{2.7}$ > 95^{th} percentile and/or LVM/BSA > 95^{th} percentile[16] and/or LVM relative to eLBM > 95^{th} percentile for age and sex.[17]

We estimated LBM using sex-specific equations that is validated for children older than 5 years.[17]

The equation for male subjects is: ln (LBM) = -2.8990 + 0.8064 × ln (height) + 0.5674 × ln (weight) + 0.0000185 $weight^2$ - 0.0153 × (BMI Z score) ^{2} + 0.0132 × age.

The equation for female subjects is: ln (LBM) = -3.8345 + 0.954 × ln (height) + 0.6515 × ln (weight) - 0.0102 × (BMI Z score).[2]

Assessment of Serum H-FABP and PAPP-A Level. Serum thiamine and cTnT levels were measured prior to dialysis session and before heparin administration to avoid its impact on serum markers. Three ml of venous blood was drawn and collected in plain gel separator vacationer and immediately centrifuged for serum separation. Serum was stored at -80ºC till the time for assessment. Steps of assay were done according to the recommendations of the manufacturers. PAPP-A level was determined using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) from Glory Science Co., Ltd (USA). H-FABP was measured using ELISA kit (Wuhan EIAab Science Co., Ltd, China).

Statistical Design. Data was analyzed using Statistical Package for the Social Science (SPSS),

program version 16 (Inc, Chicago, Illinois, USA). Data was described in terms of mean ± standard deviation (± SD), and percentage. Chi square-test was used for comparison of qualitative data. Odds Ratios was performed for predictors of cardiac comorbidity in CKD patients. Student's T test and MannWhitney U test were used for quantitative data. Correlation was done to assess relation between clinical, echocardiographic data and cardiac biomarkers. Receiver operating characteristic curves (ROC) was used to identify sensitivity, specificity and determine optimal cut-off points of cardiac biomarkers. Significance level was taken at *P* value ≤ .05.

RESULTS

Mean age of studied children with CKD was 10.4 ± 3.2 years old nearly equal to healthy children. Sex was distributed equally in both groups with no significant statistical difference. Among CKD group the duration of dialysis ranged between 6 months and 8 years with a mean duration of 22.9 ± 16.5 months. The underlying renal pathology included atrophic kidney 30%, focal segmental glomerulosclerosis 25%, vesico-ureteric reflux and interstitial nephritis 15% (for each), nephronophthesis, nephrocalcinosis, polycystic kidney disease 5% (for each). More than two thirds (65%) of CKD children had systemic hypertension.

Table 1. Comparison of Clinical, Laboratory, and Echocardiographic Data of the Studied Children

Variables	CKD (n = 20)	Control (n = 20)	Independent T test / Mann-Whitney U test Chi-square test	
			t/X^2	*P*
Age (years)	10.1 ± 3.370	10.4 ± 2.927	-0.301	> .05
Gender				
Male	10 (50%)	10 (50%)	0.000	> .05
Female	10 (50%)	10 (50%)		
Weight (z-score)	-0.707 ± 0.715	0.706 ± 0.699	-6.320	< .001*
Height (z-score)	-0.574 ± 0.896	0.573 ± 0.746	-4.401	< .001*
LBM (kg)	18.825 ± 4.776	26.815± 4.694	-5.335	< .001*
H-FABP (pg/ml)	17.9763 ± 3.420	6.214 ± 7.288	6.534	< .001*
PAPP-A (pg/ml)	153.16 ± 70.425	6.291 ± 2.807	9.319	< .001*
IVSd (cm)	0.824 ± 0.0 89	0.6385 ± 0.063	7.577	< .001*
IVSs (cm)	0.967 ± 0.233	0.9685 ± 0.152	-0.024	> .05
LVIDd (cm)	3.872 ± 0.687	3.805 ± 0.566	0.334	> .05
LVIDs (cm)	2.558 ± 0.444	2.357 ± 0.440	1.438	> .05
LVPWd (cm)	0.802 ± 0.119	0.682 ± 0.111	3.300	< .05*
LVPWs (cm)	1.164 ± 0.206	1.164 ± 0.122	-0.009	> .05
LVEDV (ml)	69.822 ± 23.678	65.305 ± 22.229	0.622	> .05
LVESV (ml)	24.644 ± 10.335	20.94 ± 7.483	1.298	> .05
LVEF%	60.709 ± 12.031	65.555 ± 3.802	-1.717	> .05
LVFS%	34.457 ± 7.361	35.915 ± 3.647	-1.288	> .05
LVSV (ml)	44.869 ± 15.260	43.07 ± 14.938	0.377	> .05
MV E vel (m/s)	0.961 ± 0.154	0.956 ± 0.075	0.117	> .05
MV A vel (m/s)	0.699 ± 0.159	0.747 ± 0.172	-0.913	> .05
MV E/A ratio	1.422 ± 0.296	1.332 ± 0.266	1.000	> .05
PASP (mmHg)	36.5 ± 9.746	22.7 ± 2.617	6.115	< .001*
LVM (gm)	95.36 ± 29.694	66.81 ± 13.488	3.915	< .001*
LVM/BSA	101.2 ± 33.248	54.6 ± 11.909	5.901	< .001*
$LVM/Ht^{2.7}$	49.66 ± 17.974	25.825 ± 6.881	5.538	< .001*
RWT	0.439 ± 0.141	0.3665 ± 0.091	1.935	> .05

CKD: chronic kidney disease; LBM: lean body mass; H-FABP: heart type fatty acid binding protein; PAPP-A: pregnancy associated plasma protein-A; IVSd: interventricular septum (diastole); IVSs: interventricular septum (systole); LVIDd: left ventricular internal dimension (diastole); LVIDs: left ventricular internal dimension (systole); LVPWd: left ventricular posterior wall (diastole); LVPWs: left ventricular posterior wall (systole); LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVEF%: left ventricular ejection fraction, LVFS%: left ventricular fraction of shortening; LVSV: left ventricle stroke volume; MV E vel: mitral valve early diastolic velocity; MV A vel: mitral valve atrial contraction diastolic velocity; TV E vel: tricuspid valve early diastolic velocity; TV A vel: tricuspid valve late diastolic velocity; PASP: pulmonary artery systolic pressure; LVM: left ventricular mass; LVM/BSA: left ventricular mass indexed to body surface area; $LVM/Ht^{2.7}$: left ventricular mass indexed to height $^{2.7}$; RWT: relative wall thickness.

Over 2 years follow up showed that 60% of the CKD children developed clinical manifestation of heart failure that needed hospital admission to pediatric intensive care; 25% of them died due to cardiovascular events.

Concerning clinical, laboratory investigations and echocardiographic findings of the studied children; CKD children had a significant increased serum H-FABP and PAPP-A and LVM index than healthy controls as demonstrated especially in children who developed cardiovascular morbidities in Table 1 and 2.

Elevated H-FABP and PAPP-A serum levels increase the risk of adverse cardiovascular outcomes in CKD children by 33 and 9.8 times respectively. While, LVM indexed to BSA and hypertension increase the risk of adverse cardiovascular outcomes 21 and 13 times respectively as shown in Table 3.

It was found that serum levels of H-FABP and PAPP-A had significant positive correlation with the duration of dialysis, blood pressure and LVM indexed to either BSA or hight$^{2.7}$ as shown in Table 4.

ROC curve was plotted according to the data of the studied groups. AUC was 0.896when the level of H-FABP was > 17.4 pg/mL with 91.7% sensitivity and 75% specificity to predict cardiac morbidity in patients with CKD. While, PAPP-A has 75% sensitivity and 87.5% specificity at cut off point ≥ 154.4 pg/mL with AUC was 0.823 as demonstrated in Figure 1.

Table 2. Comparison of Clinical, Laboratory, and Echocardiographic Data Between Chronic Kidney Disease Patients With and Without Cardiovascular Morbidity

Variables	CKD With Cardiovascular Morbidity (n = 12)	CKD Without Cardiovascular Morbidity (n = 8)	Independent T Test / Mann-Whitney U Test/ Chi Square Test	
			t	*P*
Age (years)	10.666 ± 3.366	9.875 ± 2.949	0.555	> .05
Duration of Dialysis (month)	26.416 ± 23.055	17.25 ± 11.793	3.843	< .05*
LBM (kg)	18.3 ± 3.845	19.612 ± 6.125	-0.539	> .05
Hypertension (n, %)	10 (83.3%)	3 (37.5%)	4.432	< .05*
H-FABP (pg/mL)	19.971 ± 1.544	14.986 ± 3.313	3.977	< .05*
PAPP-A (pg/mL)	180.585 ± 63.520	124.527 ± 50.828	2.183	< .05*
IVSd (cm)	0.845 ± 0.098	0.797 ± 0.082	1.168	> .05
IVSs (cm)	1.017 ± 0.257	0.892 ± 0.183	1.26	> .05
LVIDd (cm)	4.114 ± 0.578	3.632 ± 0.515	1.949	> .05
LVIDs (cm)	2.661 ± 0.443	2.403 ± 0.425	1.303	> .05
LVPWd (cm)	0.827 ± 0.101	0.764 ± 0.138	1.118	> .05
LVPWs (cm)	1.164 ± 0.199	1.159 ± 0.221	0.056	> .05
LVEDV (mL)	76.733 ± 24.942	59.437 ± 18.425	1.781	> .05
LVESV (mL)	27.067 ± 10.830	21.007 ± 9.008	1.358	> .05
LVEF %	57.833 ± 12.821	65.075 ± 9.956	-1.418	> .05
LVFS %	33.808 ± 7.648	35.437 ± 7.304	-0.48	> .05
LVSV (mL)	49.592 ± 16.058	37.787 ± 11.464	1.917	> .05
MV E Vel (m/s)	0.908 ± 0.079	1.05 ± 0.207	-1.847	> .05
MV A Vel (m/s)	0.686 ± 0.141	0.716 ± 0.196	-0.377	> .05
MV E/A Ratio	1.37 ± 0.292	1.498 ± 0.305	-0.94	> .05
PASP (mmHg)	41.583 ± 8.117	28.875 ± 6.599	3.843	< .05*
LVM (gm)	106.442 ± 30.026	78.737 ± 21.221	2.417	< .05*
LVM/BSA	114.333 ± 33.246	81.500 ± 22.897	2.615	< .05*
LVM/Ht$^{2.7}$	57.433 ± 17.864	38 ± 10.791	3.029	< .05*
RWT	0.409 ± 0.062	0.484 ± 0.209	-0.98	> .05
LVH (n, %)	10 (83.3%)	2 (25%)	6.806	< .05*

*$P \leq .05$ significant

CKD: chronic kidney disease; H-FABP: heart type fatty acid binding protein; PAPP-A: pregnancy associated plasma protein-A; IVSd: interventricular septum (diastole); IVSs: interventricular septum (systole); LVIDd: left ventricular internal dimension (diastole); LVIDs: left ventricular internal dimension (systole); LVPWd: left ventricular posterior wall (diastole); LVPWs: left ventricular posterior wall (systole); LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVEF%: left ventricular ejection fraction, LVFS%: left ventricular fraction of shortening; LVSV: left ventricle stroke volume; MV E vel: mitral valve early diastolic velocity; MV A vel: mitral valve atrial contraction diastolic velocity; TV E vel: tricuspid valve early diastolic velocity; TV A vel: tricuspid valve late diastolic velocity; PASP: pulmonary artery systolic pressure; LVM: left ventricular mass; LVM/BSA: left ventricular mass indexed to body surface area; LVM/Ht$^{2.7}$: left ventricular mass indexed to height $^{2.7}$, LBM: lean body mass; RWT: relative wall thickness, LVH: left ventricular hypertrophy.

Table 3. Odds Ratio for Some Factors Predicting Cardiovascular Morbidity in Chronic Kidney Disease Children on Regular Heamodialysis

Variables	Odd Ratio (95% Confidence Interval)
H-FABP (> 17.4 pg/mL)	33 (2.5 - 443.6)
PAPP-A (> 154.4 pg/mL)	9.8 (0.9 - 107)
LVM/BSA (> 95th Percentile)	21 (1.8 - 248)
LVM/Ht$^{2.7}$ (> 95th Percentile)	5 (0.6 - 39)
LVM/LBM (> 95th Percentile)	15 (1.7 - 136.2)
Hypertension	13 (2 - 85)

H-FABP: heart type fatty acid binding protein; PAPP-A: pregnancy associated plasma protein-A;LVM/BSA: left ventricular mass indexed to body surface area; LVM/Ht$^{2.7}$: left ventricular mass indexed to height $^{2.7}$; LVM/LBM: left ventricular mass relative to lean body mass (LBM) LVH: left ventricular hypertrophy

DISCUSSION

End stage renal disease exposes myocardium to pressure and volume overload. In addition it is associated with non-hemodynamic factors that adversely impair cardiac function.[18] Hemodialysis induces repetitive hemodynamic instability with subsequent myocardial ischemia that accelerates myocardial injury in CKD children. Releasing intracellular proteins from the damaged cardiomyocytes into the circulation and assaying these circulating molecules is considered as predictors for estimating the extent of cardiac damage.[19]

Over 2 years follow up of CKD children in our nephrology unit, the incidence of cardiovascular events was 60%; 15% of them died. In accordance, Chavers et al[20] revealed that 31.2% of dialysis children aged ≤ 19 years developed cardiac-related events. Moreover, Oh et al[21] found that 50% of CKD subjects died either due to cardiovascular or cerebrovascular events.

The present study clarified that hypertension and LVM index were higher among children who developed cardiac morbidity. LVM indexed to BSA and hypertension increases the odds of occurrence of cardiac morbidity by 21 and 13 times respectively.

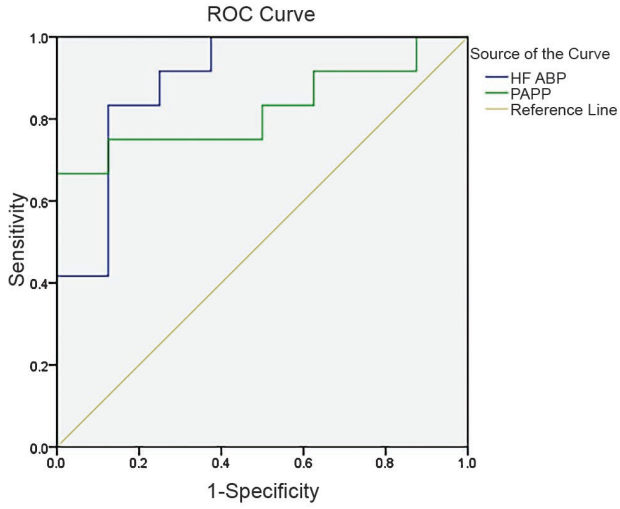
Our findings came in accordance with Rinatet et al[22] who found significant elevated blood pressure and LVM index in CKD children specially those who developed cardiovascular morbidity. Subclinical myocardial ischemia can occur during dialysis process due to ultrafiltration volume and blood pressure changes. The repetitive nature of myocardial ischemic injury has cumulative effect, leading to progressive ventricular dysfunction.[23] Elevated LVM could reflect cardiac remolding process and represent a strong independent predictor for adverse cardiac outcomes even in those without LVH. Zoccali et al[24] reported that elevated LVM is associated with (50% and 85%) mortality risk and cardiovascular event risk respectively in CKD children on hemodialysis.

Table 4. Correlation Between Clinical, Echocardiographic Data, and Cardiac Biomarkers Serum Level Among Children with Chronic Kidney Disease on Regular Hemodialysis

Variables	HFABP		PAPP	
	r	P	r	*P*
Duration of dialysis (month)	0.5	< .05*	0.7	< .05*
Systolic BI/P (z-score)	0.7	< .05*	0.6	< .05*
Diastolic BI/P (z-score)	0.7	< .05*	0.6	< .05*
IVSd (cm)	0.4	> .05	0.4	> .05
IVSs (cm)	0.1	> .05	0.2	> .05
LVIDd (cm)	0.4	> .05	0.4	> .05
LVIDs (cm)	0.4	> .05	0.5	< .05*
LVPWd (cm)	0.4	> .05	0.3	> .05
LVPWs (cm)	0.1	> .05	0.2	> .05
LVEF%	-0.5	< .05*	-0.4	> .05
LVFS%	-0.4	> .05	-0.4	> .05
LVSV (ml)	0.3	> .05	0.3	> .05
LVM/BSA	0.6	< .05*	0.5	< .05*
LVM/Ht$^{2.7}$	0.6	< .05*	0.6	< .05*
RWT	0.2	> .05	-0.2	> .05

*$P \leq .05$ Significant

BI/P: blood pressure; H-FABP: heart type fatty acid binding protein; PAPP-A: pregnancy associated plasma protein-A; IVSd: interventricular septum (diastole); IVSs: interventricular septum (systole); LVIDd: left ventricular internal dimension (diastole); LVIDs: left ventricular internal dimension (systole); LVPWd: left ventricular posterior wall (diastole); LVPWs: left ventricular posterior wall (systole); LVEF%: left ventricular ejection fraction, LVFS%: left ventricular fraction of shortening; LVSV: left ventricle stroke volume; LVM/BSA: left ventricular mass indexed to body surface area; LVM/Ht$^{2.7}$: left ventricular mass indexed to height $^{2.7}$, LBM: lean body mass; RWT: relative wall thickness.



Variables	Cutoff	AUC	Senstivity%	Specificity%	PPV%	NPV%
H-FABP (pg/mL)	> 17.4	0.896	91.7	75.0	44.9	99
PAPP-A (pg/mL)	> 154.4	0.823	75.0	87.5	34.1	95

Figure 1. Receiver operating characteristic curves for prediction of adverse cardiovascular outcomes in CKD Children
AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value; H-FABP: heart type fatty acid binding protein; PAPP-A: pregnancy associated plasma protein-AA

The current study detected significant positive correlation between circulating cardiac biomarker H-FABP with clinical and echocardiographic indicators of left ventricular performance including LVM index in CKD children, and its levels significantly elevated in those with cardiac morbidity.

Positive correlation between H-FABP and systemic blood pressure reflects ventricular remolding in response to pressure overload and clarifies its role in cardiomyocyte response to stress injury and volume overload in CKD patients. Furthermore, elevated H-FABP increases the odds of occurrence of cardiac events by 33 times suggesting its value as prognostic predictor.

In agreement, Lippi et al[25] reported that H-FABP was correlated positively with the severity of cardiac dysfunction and the progress of myocardial ischemia. Uremic cardiomyopathy is a serious complication of CKD and it may be possible that some of the leakage of H-FABP could reflect sub-clinical myocardial injury demonstrated that serum H-FABP levels elevated in children with congestive heart failure and are closely related to its severity.[26]

H-FABP is an intra-cytoplasmic protein that is that is released earlier than Troponin because it did not bind to protein and has smaller size (14–15 kDa) than troponin I or T (21–37 kDa). Even though H-FABP is eliminated by the kidneys, its serum level is not affected by dialysis. [27] The present study revealed higher level of PAPP-A in children with CKD and CVD than those without. Also, its elevation increases the odds of occurrence of cardiac morbidity by 9.8 times. PAPP-A has significant positive correlation with LVM index, hypertension and duration of hemodialysis suggesting its involvement in cardiomyocyte response to stress injury and volume overload in CKD children.

In accordance, D'Eliaet et al[28] demonstrated that elevated PAPP-A is caused by activation of endogenous heart regeneration in response to injury. Nilssonet et al[29] revealed that elevated PAPP-A is associated with worse survival in CKD patients on regular hemodialysis after adjustment for cardiovascular risk factors.

Fialová et al[30] stated that elevated serum PAPP-A in CKD subjects on regular hemodialysis resulted from high oxidation stress and inflammation in such subjects. However, its level is not affected by hemodialysis process due to its high molecular weight therefore cannot be removed during dialysis.

PAPP-A functions as a protease and cleaves IGFBP-4 to release IGF-1, thereby increasing the local IGF-1 activity. Myocardial damage alters the

IGF regulatory system leading to release of PAPP-A to increase the IGF-1 level in the myocardial tissue. However, it isn't clear whether PAPP-A expression is caused by tissue repair or pathological response.[31]

Few studies are available for evaluating the prognostic value of PAPP-A with small sized patient sample and short follow-up period. Kalousová et al[32] followed up 40 hemodialysis patients for 20 months and demonstrated higher PAPP-A levels at the initial evaluation in patients who died compared to survivors. Lauzurica et al[33] concluded that the pre transplant serum concentration of PAPP-A serves as a predictor of post-transplant cardiovascular events and chronic allograft nephropathy. The major limitation of this study is small number of included patients; however, we could detect significant differences in circulating biomarker levels that strongly correlated with both echocardiographic findings and cardiovascular morbidity in CKD children. Also, LVM was assessed using echocardiography as MRI is expensive and not available in hospital of study.

CONCLUSIONS

These findings indicate that monitoring cardiac morbidity using these cardiac biomarkers may be useful in clinical practice as indicator of cardiovascular mortality and morbidities in CKD children.

RECOMMENDATIONS

In light of these findings, H-FABP and PAPP-A may be suitable screening cardiac biomarkers in CKD children on dialysis aiming to prevent future cardiovascular events. This study encourages use of these markers in routine clinical practice for early detection and follows up of myocardial impairment along with timely intervention, in turn may aid in decreasing mortality and morbidity among CKD subjects. Also, larger cohorts are required to assess these emerging biomarkers.

SOURCES OF FUNDING

None

CONFLICTS OF INTEREST

No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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Received July 2018
Revised September 2018
Accepted October 2018