ORIGINAL ARTICLE

Galectin-3 as an early marker of diastolic dysfunction in children with end-stage renal disease on regular hemodialysis

Akram Elsadek[1], Mohamed Ibrahim[2], Asmaa Adel El Fallah[3], Mohamed Elian[2], Salem Elsayed Deraz[4]

[1]Department of Pediatrics, Faculty of Medicine, Benha University, Benha, Egypt, [2]Department of Cardiology, Faculty of Medicine, Benha University, Benha, Egypt, [3]Department of Clinical Pathology, Faculty of Medicine, Benha University, Benha, Egypt, [4]Department of Pediatrics, Faculty of Medicine, Menoufia University, Shebin El-Kom, Menoufia, Egypt

ABSTRACT

Introduction and Aim : **Diastolic dysfunction is a common finding in end-stage renal disease (ESRD) on regular hemodialysis (HD). Galectin-3 (Gal-3) has emerged as an early biomarker with diagnostic and prognostic values in cardiac dysfunction with reduced or preserved ejection fraction. We aimed to assess the correlation between Gal-3 levels and diastolic dysfunction in children with ESRD on regular HD.**

Materials and Methods : **Gal-3 levels were assessed in 67 patients on regular HD and 67 healthy controls. Conventional echo-Doppler imaging and tissue-Doppler imaging were done to all patients and control groups. Patients were split into two categories: with or without diastolic dysfunction, based on the early diastolic transmitral velocity to early diastolic mitral annular velocity (E/E') whether more or less than 15, respectively**

Results : **Plasma Gal-3 levels in ng/ml were 16.7 (12.0–22.0) in healthy controls, 15.7 (10.5–22.0) in patients on HD without diastolic dysfunction, and 23.4 (13.4–25.0) in patients on HD with diastolic dysfunction. Gal-3 levels were significantly higher in HD patients with left ventricular diastolic dysfunction (LVDD). Both uni- and multivariate logistic regression analyses revealed that low left ventricular Tei index, low early diastolic mitral annular velocity of lateral wall wave, low early diastolic mitral annular velocity of septal wall wave, high septal early diastolic transmitral velocity to early diastolic mitral annular velocity of lateral wall (E/E') ratio, and high Gal-3 are significant predictors for LVDD in the whole study group. Furthermore, there was a significant positive correlation between the Gal-3 and the grade of diastolic dysfunction. The cut of point of diagnostic accuracy of serum Gal-3 in diastolic dysfunction in HD children was 20.12 with a sensitivity of 93.3 and a specificity 78.4.**

Conclusions : **Gal-3 is a potential early biomarker that can be used in early diagnosis and grading of diastolic dysfunction in ESRD children on regular HD.**

Keywords : Children, diastolic dysfunction, early marker, galectin-3, hemodialysis

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INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a widespread disease and its prevalence in increasing. Myocardial stiffness from hypertrophy and fibrosis is pivotal to the occurrence of diastolic dysfunction, which is the typical characteristic of this kind of myocardial disease. Children with end-stage renal disease (ESRD) on regular hemodialysis (HD) have a significantly increased cardiovascular mortality compared to the general community, contributing to nearly 40% of all-cause mortality in these patients.[1,2] Diastolic dysfunction in dialysis patients exists before the presence of systolic heart failure (HF) and it has shown to provide prognostic information regarding cardiovascular mortality.[3,4] Therefore, early assessment of left ventricular (LV) diastolic dysfunction is of significant importance in the diagnosis and risk stratification of these cases, especially in those with normal systolic function.[3] Echocardiography is a safe and effective method for the assessment of LV diastolic function.[4]

Serum biomarkers such as troponin I, troponin T, and amino-terminal pro-brain natriuretic peptide (NT-Pro BNP) are useful additional tools for understanding the pathogenesis and assessing prognosis and risk stratifying patients. Galectin-3 (Gal-3) is a new biomarker that is suggested to be one of the factors implicated in the pathophysiology of HFpEF, such as chronic inflammation, fibrosis, tissue repair and scarring, and eventually ventricular remodeling. Gal-3 is a β-galactoside-binding protein produced by activated macrophages.[5] It is transcribed by the gene (LGALS3) on chromosome 14, locus q21–q22, and expressed in the nucleus and mitochondria.[5] In the myocardium, Gal-3 assists transforming growth factor β (TGFβ) to increase cell cycle (cyclin D1) of myofibroblasts, which results in their proliferation and synthesis of procollagen.[6] Recently, Gal-3 has been linked to HF development, severity, and prognosis.[7,8]

In this study, we evaluated the potential role and importance of Gal-3 as an early biomarker of asymptomatic diastolic dysfunction in children with ESRD on regular HD.

MATERIALS AND METHODS

We carried out this prospective study at both Benha and Menoufia University Hospital; Egypt, from January 2018 to July 2020. Sixty-seven children with ESRD on regular HD were included in the study and 67 age- and sex-matched healthy children were selected as controls. The patients with ESRD were further classified into two groups based on the presence or absence of diastolic dysfunction. Patients with atrial fibrillation, LV ejection fraction <50%, valvular heart disease, pericardial disease, and restrictive cardiomyopathy were excluded. Relevant clinical data of all patients and control group were collected. Blood samples, collected from both patients and controls, were preserved and processed for laboratory evaluation. Conventional transthoracic echocardiography-Doppler imaging and tissue-Doppler imaging (TDI) were performed in all patients. Written informed consent was obtained from all participants for their inclusion in the study. The study was approved by the research and ethical committees of both Benha and Menoufia Universities.

Transthoracic echocardiography

A detailed transthoracic echocardiographic examination was performed in all the patients using Philips HD 11 machine with the multifrequency probes S8 (3–8 MHz) and S4 (1–4 MHz). Patients on HD were examined by echocardiography between HD sessions, usually 2 h after dialysis, in order to avoid acute volume changes. None of the patients were critically ill at the time of the investigation.

According to standard techniques, a comprehensive 2D echocardiography, color, and pulse- and continuous-wave Doppler echocardiogram was done. Several conventional parameters of LV diastolic function were assessed including transmitral E-wave velocity, E-wave deceleration time (DT), and late diastolic wave (A) velocity. Doppler time intervals were calculated from the mitral inflow and LV outflow velocity time intervals. Isovolumic contraction time (IVCT), ejection time (ET), and the isovolumic relaxation time (IVRT) were estimated. Then, myocardial performance index (MPI) was measured as the sum of IVCT and IVRT, dividing it by ET. LV mass index (LVMI) was calculated by Devereux's formula using the M-mode of the parasternal long-axis view and indexed to body surface area.[9] Relative wall thickness was measured by the formula: $(2 \times$ posterior wall thickness in diastole)/LV internal dimension in diastole.[9]

Furthermore, TDI was documented by high frame rate (≥100 frames/s) from the apical 4-chamber side to evaluate myocardial velocities. Peak annular early diastolic velocity (E′) was evaluated by 2 annular LV segments (septal and lateral). Normal diastolic function was identified when medial mitral annular e′ ≥8 cm/s and lateral mitral annular e′ ≥10 cm/s. Diastolic dysfunction was diagnosed if the medial annular e′ <8 cm/s and lateral annular e′ <10 cm/s. Further categorization of diastolic dysfunction into severity Grades 1, 2, or 3 was performed using the mitral early/late diastolic mitral flow (E/A) ratio, E-wave deceleration time, average E/e′ value, and peak pulmonary systolic pressure. The ratio of early diastolic transmitral velocity to early diastolic mitral annular velocity of lateral wall (E/E′) was measured as an estimate of LV filling pressure, and LV diastolic dysfunction (LVDD) was defined as E/E′

≥15.0.[10] Measurements of the myocardial velocities were calculated on three heart beats and the average of the three readings was measured. All patients had regular rhythm at the time of examination.

Myocardial performance index measurement
Doppler time intervals were measured from mitral inflow and LV outflow Doppler tracings. The interval from cessation to onset of mitral inflow is equal to the sum of isovolumic contraction time (ICT), ET, and isovolumic relaxation time (IRT). ET is derived from the duration of the LV outflow Doppler velocity profile. The sum of ICT and IRT was obtained and the MPI was calculated.[11]

Limitation of Doppler in patients with renal failure

In patients with ESRD, because of the anemia, systemic hypertension, volume overload, and the presence of an AVF with high-flow rates, LV systolic and diastolic diameters, wall thickness, and cardiac output are increased and indirectly EF is decreased. Several studies have shown that patients with ESRD before and on dialysis had higher LV volumes and dimensions.[12] The echo-Doppler studies were done 2 h after the dialysis sessions to avoid the effect of volume overload or medications on Doppler results.

Galectin-3 level
Blood samples from both patients and controls were collected for the measurement of routine renal functions and Gal-3 level in ethylenediaminetetraacetic acid (EDTA) plasma. Samples for Gal-3 levels were collected just before initiation of HD and stored at −80°C until being processed in the laboratory. Determination of Gal-3 was assessed using enzyme-linked immunosorbent assay (ELISA) kits (BGM Galectin-3® assay; BG Medicine, Inc., Waltham, MA, USA). The assay quantitatively measures the concentration of human Gal-3 levels in EDTA plasma. This assay has a high efficiency (lower limit of detection 1.13 ng/mL) and exhibits no cross-reactivity with collagens or other members of the galectin family. Commonly used cardiac medications do not affect the assay. Calibration of the assay was performed according to the manufacturer's recommendation and the values were normalized to a standard curve.[13]

Principle of test
ELISA is a solid phase two-site enzyme immunoassay. It is done via sandwich technique where two monoclonal antibodies directed against two antigenic determinants on the galectin molecule. During incubation, galectin in the sample reacts with enzyme horseradish peroxidase (HRP)-conjugated anti-insulin antibody and anti-insulin antibody bound to microtitration well. Simple washing step removes the unbound enzyme-labeled antibody. Bound HRP complex was discovered by reaction with tetramethylbenzidine substrate. The reaction was finished by adding acid to reach a colorimetric endpoint that is read through an ELISA reader.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, using Chi-squared test (χ^2) for their analysis. Continuous data were shown as mean ± standard deviation when normally distributed or medians with lower and upper quartiles (interquartile range) when nonnormally distributed. Shapiro test of normality was used assuming normality at $P > 0.05$. Parametric variables were analyzed by Student's *t*-test for 2 independent groups, whereas nonparametric ones were analyzed by MannWhitney *U*-test. ANOVA (f) test is used for comparison between three groups having normally distributed quantitative variables. *Post hoc* test is performed after ANOVA to detect a significant difference between each pair group. Spearman's correlation coefficient (*r*) is used to measure the association between quantitative variable (Gal-3 Level) and ordinal qualitative variable (grades of diastolic dysfunction). Differences among three independent groups were compared using KruskalWallis test. Spearman's correlation coefficient (rho) was employed to test correlations between Gal-3 and other variables. Univariable and multivariable binary logistic regression analysis was run to detect the significant predictors of LVDD among HD patients. Two-sided $P \leq 0.05$ was considered statistically significant. All statistical analyses were done using SPSS versionI 18.0 (BM® SPSS® Statistics).[14]

RESULTS

Sixty-seven patients with ESRD on regular HD and 67 healthy controls were enrolled in the study. The normal cases were taken in a blinded fashion from the pediatric cardiology clinic. No statistically significant difference was detected between the two groups regarding age, gender, and weight [Table 1].

When using the definition of diastolic dysfunction as early diastolic mitral annular velocity of lateral wall (E′ lateral) <10 mm and or early diastolic mitral annular velocity of septal wall (E′ septal) <8 mm, echo-Doppler and TDI further divided the patients into two groups: Group 1 of 37 patients without LVDD and Group 2 of 30 patients with LVDD.

Gal-3 levels were nonsignificantly elevated in patients without LVDD as compared to controls [Table 1 and Figure 1]. However, the patients with LVDD had significantly high Gal-3 levels; (median and range) 23.4 (13.4–25.0) ng/ml; when compared to both controls; 16.7 (12.0–22.0) ng/ml [Table 1 and Figure 1] and patients without LVDD; 15.7 (10.5–22.0) ng/ml [Table 2].

LV end-diastolic diameter, LV end-systolic dimension, LV mass, EF, and fractional shortening were measured to evaluate the systolic function, which were normal in

both the patients and control groups. Mitral E/A ratio, LV myocardial performance index (LV Tei index), E′ lateral, E′ septal, and E/E′ ratio were measured to evaluate the diastolic function and were abnormal in patients of group 2 (patients with LVDD), with a statistically significant difference between the two groups [Table 2].

Both uni- and multivariate logistic regression analyses revealed that low LV Tie index, low E′ lateral wave, low E′ septal wave, high septal E/E′ ratio, and high Gal-3 were significant predictors for LVDD in the whole study group [Table 3].
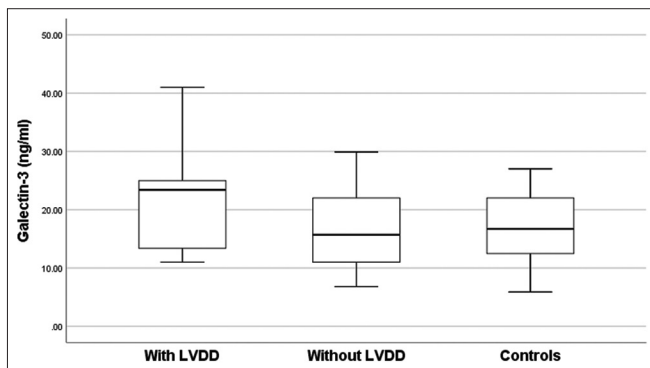

Figure 1: Box plot showing median and IQR of Galectin-3 among the studied groups. IQR: Interquartile range, LVDD: Left ventricular diastolic dysfunction

Twelve patients showed the echo-Doppler criteria of grade I diastolic dysfunction, 9 patients with grade II diastolic dysfunction, 5 patients with grade III, and 4 patients with IV diastolic dysfunction. There was a significant positive correlation between the Gal-3 and the grade of diastolic dysfunction. Grade I of diastolic dysfunction group had significantly lower mean values of Gal-3 (ng/ml) level than those with grade II, grade III, and grade IV ($P < 0.05$). Furthermore, Grade II of diastolic dysfunction group had significantly lower mean values of Gal-3 (ng/ml) level than those with grade III and IV ($P < 0.05$) [Table 4 and Figure 2].

In HD patients, LVDD was present in 30 patients. Within this set, the receiver operating characteristic curve analysis suggested that the optimum cutoff point of Gal-3 for the evaluation of LVDD was 20.12 ng/ml with sensitivity, specificity, positive predictive, and negative predictive values of 93.3, 78.4, 80, and 93.75%, respectively. Area under the curve = 0.859 [Table 4 and Figures 1, 3].

DISCUSSION

Gal-3 is considered a good recent serum biomarker for the evaluation of patients with myocardial dysfunction. The identification of its potential predictive value in HFpEF was assessed by a substudy of the

Table 1: Demographic data of the study patients and control group

Parameter	HD patients (*n*=67)	Control (*n*=67)	Test of significance	*P*
Age (years)	12.1±4.1	11.7±4	Student's "*t*"=0.57	0.569
Male (%)	40 (59.7)	37 (55.2)	χ^2=0.27	0.6
Female (%)	27 (40.3)	30 (44.8)		
Weight (kg)	35.7±10.7	39.2±10.1	Student's "*t*"=1.94	0.054
Gal-3 (ng/ml), median (IQR)	Without LVDD: 15.7 (10.5-22.0) With LVDD: 23.4 (13.4-25.0)	16.7 (12.0-22.0)	KW=11.4 *P*=0.003 (significance)	Adjusted *P* value of multiple comparisons* No LVDD-controls=0.46 LVDD-controls=0.013 No LVDD-LVDD=0.007

KW test was followed by *post hoc* multiple comparisons using Bonferroni test to detect the significant pairs. KW: Kruskal-Wallis, LVDD: Left ventricular diastolic dysfunction, IQR: Interquartile range, HD: Hemodialysis, Gal-3: Galectin-3

Table 2: Conventional echo-Doppler and Doppler-tissue-imaging findings in patients with and without diastolic dysfunction

Parameter	Group 1: Patients on HD without LVDD (*n*=37)	Group 2: Patients on HD with LVDD (*n*=30)	Student's "*t*"	*P*
LVEDD (cm)	4.2±0.52	4.4±0.7	1.3	0.19
LVESD (cm)	2.42±0.42	2.71±0.9	1.74	0.086
LVM (g)	105.8±20.5	108.9±50.4	0.34	0.73
FS (%)	35±5.15	36.5±6.03	1.09	0.27
EF (%)	67±6.5	66±8.03	0.56	0.57
Mitral E/A ratio	2.3±0.7	2.2±0.8	0.55	0.58
LV Tei index	0.41±0.10	0.32±0.11	3.5	0.001 (HS)
E′ lateral (cm/s)	12.7±2.10	7.70±2.50	8.89	<0.001 (HS)
E′ septal (cm/s)	9.72±1.4	5.72±1.41	11.6	<0.001 (HS)
Septal E/E′ ratio	12.55±1.60	18.10±1.31	15.3	<0.001 (HS)
Gal-3 (ng/ml)	15.7 (10.5-22.0)	23.4 (13.4-25.0)	Z_{MWU}=2.68	0.007 (signficance)

Z_{MWU}: *Z* value of Mann-Whitney *U*-test, LV: Left ventricular, LVEDD: LV end-diastolic dimension, LVESD: LV end-systolic dimension, LVM: LV mass, LVDD: LV diastolic dysfunction, LV Tei index: LV myocardial performance index, HS: Highly significance, EF: Ejection fraction, FS: Fractional shortening, HD: Hemodialysis, E/A: Early/late diastolic mitral flow, E′ lateral: Early diastolic mitral annular velocity of lateral wall, E′ septal: Early diastolic mitral annular velocity of septal wall, E/E′: Early diastolic transmitral velocity to early diastolic mitral annular velocity of lateral wall, Gal-3: Galectin-3

Table 3: Univariable and multivariable binary logistic regression analysis for the predictors of left ventricular diastolic dysfunction among hemodialysis patients

Parameter	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Low LV Tei index	1.62	1.12-2.57	0.001 (HS)	1.21	1.02-1.67	0.012 (significance)
Low E′ lateral (cm/s)	1.84	1.15-2.91	<0.001 (HS)	1.39	1.1-2.01	0.006 (significance)
Low E′ septal (cm/s)	1.97	1.09-2.61	<0.001 (HS)	1.3	1.05-2.14	0.01 (significance)
High septal E/E′ ratio	2.04	1.2-2.79	<0.001 (HS)	1.47	1.1-2.55	0.002 (significance)
High Gal-3 (ng/ml)	1.42	1.03-2.07	0.007 (significance)	1.15	1.03-1.71	0.031 (significance)

OR: Odds ratio, CI: Confidence interval, HS: Highly significance, LV: Left ventricular, LV Tei index: LV myocardial performance index, E′ lateral: Early diastolic mitral annular velocity of lateral wall, E′ septal: Early diastolic mitral annular velocity of septal wall, E/E′: Early diastolic transmitral velocity to early diastolic mitral annular velocity of lateral wall, Gal-3: Galectin-3, DTI: Doppler tissue imaging

Table 4: Relationship between grades of diastolic dysfunction and galectin-3 (ng/ml) level

Grades of diastolic dysfunction	Gal-3 (ng/ml), mean±SD	ANOVA test and *P*	*Post hoc* test
Grade I (*n*=12)	15.2±2.4	Test=10.39	I versus II=0.02
Grade II (*n*=9)	17.9±2.5	*P*<0.001	I versus III<0.001
Grade III (*n*=5)	20.8±2.1		I versus IV<0.001
Grade IV (*n*=4)	22.0±2.9		II versus III=0.04
			II versus IV=0.01
			III versus IV=0.48

SD: Standard deviation, Gal-3: Galectin-3

Figure 2: Correlation between grades of diastolic dysfunction and Galectin-3 (ng/ml) level

Pro-BNP in patients of dyspnea in the emergency department (PRIDE) trial, where Gal-3 serum levels were strongly correlated with echocardiographic parameters of diastolic dysfunction.[15] The clinical guidelines issued by the American Heart Association/American College of Cardiology emphasized the efficiency of Gal-3 as a predictor of mortality and hospitalization in cases with HF.[16] Gal-3 level directly reflects abnormalities in LV diastolic function or cardiac fibrosis and it may be a sensitive indicator for diagnosis.[17] It was independently correlated with GFR in cases with HF,[18] and its role in detecting HFpEF in patients undergoing HD was emphasized by Gurel *et al.*[19]

The efficiency of new serum biomarkers in assessment of HF or diastolic dysfunction in children is usually derived from adult studies. However, in this study, we intended to find out the role of Gal-3 in evaluating diastolic dysfunction in children on regular HD (as diastolic dysfunction is common in this subset of patients). In our study, Gal-3 levels were significantly higher in HD patients with LVDD. After adjusting for age, sex, body mass index, and other demographics, both uni- and multivariate logistic regression analyses revealed that low LV Tei index, low E′ lateral wave, low E′ septal wave, high septal E/E′ ratio, and high Gal-3 are significant predictors for LVDD in the whole study group [Table 3]. Furthermore, there was a significant positive correlation between the Gal-3 and the grade of diastolic dysfunction [Table 4 and Figure 2].

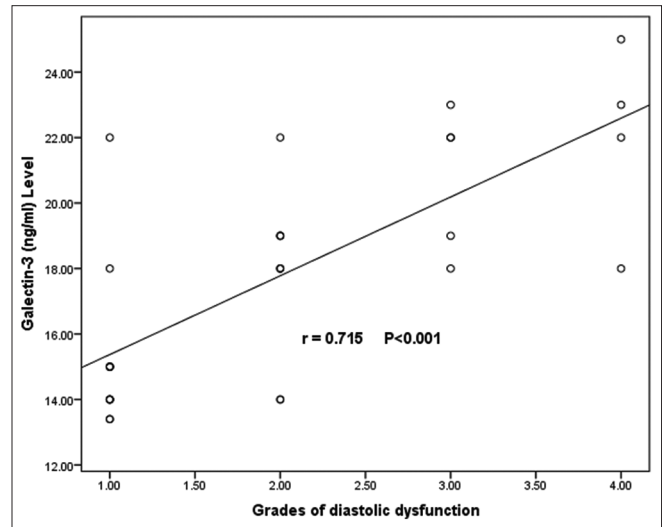Our study agrees with that of Gurel *et al.*,[19] who evaluated the relation between Gal-3 and LVDD in cases with ESRD on regular HD, who found a significant correlation between plasma Gal-3 levels and E/E′, E′, and LA volume index in their patients. Other diastolic indicators were not significantly associated with Gal-3 in the study.

Ansari *et al.*[20] demonstrated that Gal-3 level reflects the different grades of diastolic dysfunction with the highest level in Grade III and the lowest in Grade I, which goes with our observation that Gal-3 is correlated more with severe diastolic dysfunction [Table 4 and Figure 2]. The level of Gal-3 in patients with Grade I diastolic dysfunction was 15.2 ± 2.4 [Table 4]; however, these results are similar to normal controls with estimated Gal 3 level of 12.0–22.0 [Table 1], and according to these results, Gal-3 measurements are not useful to differentiate Grade I diastolic dysfunction from normal, since the values are quite overlapping.

Gal-3 and NT-pro BNP measurements were increased in patients with HFpEF in relation to control group in a study conducted by Polat *et al.*[21] They found that Gal-3 correlated positively with NT-proBNP, left atrial volume index, LVMI, and E/E′.

Table 5: Diagnostic accuracy of serum galactin-3 in diastolic dysfunction in hemodialysis children

AUC	95% CI	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
0.859	0.818-0.90	20.12	93.3%	78.4%	80%	93.75%	86.6%

AUC: Area under curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value
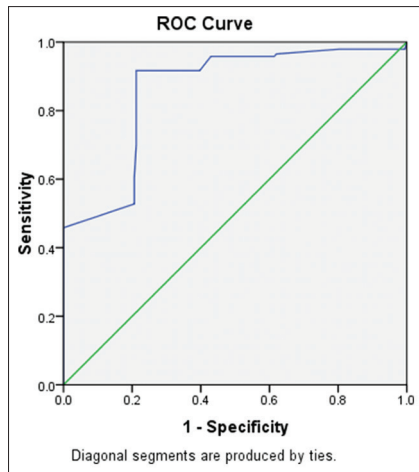

Figure 3: ROC curve analysis for the performance of plasma galectin-3 in prediction of LVDD. ROC: Receiver operating characteristic, LVDD: Left ventricular diastolic dysfunction

In our study, the cut of point of diagnostic accuracy of serum Gal-3 in diastolic dysfunction in HD children was 20.12 with a sensitivity of 93.3 and a specificity 78.4 [Table 5]. In other study done in adult patients with ESRD, Gal-3 above a median of 13.8 ng/mL independently predicted all-cause mortality in a study of 419 patients hospitalized with HF and LVEF >45%.[7]

Several other clinical studies have evaluated the relationship between Gal-3 levels and LVDD. In the 592-patient COACH study conducted by de Boer *et al*.,[22] increased Gal-3 levels were clarified as a prognostic marker in patients with HF with preserved or reduced ejection fraction, particularly in patients with HFpEF. In a subgroup analysis of 115 patients who underwent detailed echocardiography and Gal-3 measurements, Gal-3 levels were found to be correlated with diastolic parameters E/E' and E', whereas no correlation was found with E/A, early deceleration time, left atrial volume (LAV), and LVMI. Therefore, Gal-3 may be useful for early detection, risk stratification, and possible therapeutic targeting of cases with early or established HFpEF.[23]

On the other hand, recently, Rabkin and Tang[24] in their study of the utility of three biomarkers in differentiating HF with reduced ejection fraction (HFrEF) from HFpEF found no significant differences between Growth Differentiation factor-15, Gal-3, and sST2 in cases with HFpEF vs HFrEF.

The correlation between cardiac diastolic function indicators and Gal-3 levels was established in our population.

CONCLUSION

In the pediatric patients, Gal-3 plays an important role as an early biomarker in the assessment of LVDD in children with ESRD on HD.

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Conflicts of interest

There are no conflicts of interest.

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