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Electrocardiographic Changes and Holter Abnormalities in Children With Predialytic Chronic Kidney Disease

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ABSTRACT
Background: Cardiovascular disease (CVD) remains the primary cause of mortality for patients with early-onset chronic kidney disease (CKD), despite improvements in subject survival over the past several decades. Additionally, there is a dearth of research on CVD in children. **Objectives:** This research aimed to study the electrocardiographic abnormalities and Holter findings in children with predialytic CKD. **Subjects and methods:** A cross-sectional study that was conducted on 50 children with predialytic CKD through the period from November, 2022 to November, 2023. Data were collected from children through personal interviews with their parents or care givers and assessment of their anthropometric measures, laboratory investigations, echocardiography, ECG and holter study.
Results: CKD stage 5 showed the highest percentage of abnormalities in Echocardiography and ECG results, which showed a statistically significant relationship to the stages of CKD. Left ventricular hypertrophy was the main echocardiographic abnormality while prolonged QTc duration and sinus tachycardia were the main ECG abnormalities. There was a statistically significant variation between CKD stages as regards heart rate variability parameters, with CKD stage 5 participants having the lowest heart rate variability parameters as regards PNN50, rMSSD, SDNN at 5.078 ± 8.12, 29 ± 20.89, and 34.11 ± 17.55 respectively. Also, there was statistically significant difference between CKD stages as regards Hct and phosphorus level. **Conclusion:** Children in the fifth stage of chronic renal disease had the highest incidence of abnormalities observed by echocardiography, electrocardiography, and holter monitoring where patients in CKD stage 5 had the lowest heart rate variability values.
Keywords: Chronic kidney disease, Holter monitoring, Electrocardiographic, Predialytic chronic kidney disease children.

INTRODUCTION
CKD is defined as kidney damage that lasts more than three months as a result of structural or functional abnormalities, with or without a reduced GFR. The frequency of CKD in children has steadily grown during the last two decades. CKD in children is predominantly caused by kidney and urinary tract abnormalities, hereditary conditions, and glomerulopathy. Early-stage CKD is characterized by a number of changes in cardiovascular structure and function, most likely as a result of an attempt to adjust the hemodynamic and biochemical abnormalities of the disease. According to recent research, fibroblast growth factor 23 is correlated with a lower glomerular filtration rate (GFR) and may cause myocyte hypertrophy, which might lead to LVH [(1)]. CVD remains the primary cause of mortality for children with end-stage renal disease, despite improvements in the previous few decades in the survival of individuals with early onset CKD. The most significant risk factor for CVD in the early stages of CKD is hypertension. Nevertheless, anemia, mineral bone disease, and fluid overload are the primary concerns during dialysis. Children with stage 5 chronic kidney disease have been documented to exhibit arrhythmias, valvular heart disease, cardiomyopathy, and sudden cardiac death [(1)].

Patients diagnosed with early CKD are advised to modify their lifestyle and adhere to medication regimens as preventive measures against cardiovascular disease and the progression of CKD. In the case of advanced CKD, preparation for renal replacement therapy (RRT) or conservative care is advised [(2)]. The risk of CKD and mortality is greatly increased by CKD [(3)]. Kidney Disease Improving Global Outcomes offers advice for managing the most frequent CVD risk factors in children with CKD [(4)].

Standard 12-lead electrocardiogram and holter monitoring are a cost-effective diagnostic tools utilized for identification of cardiovascular disease. The electrocardiogram (ECG) plays a critical role in the identification of myocardial ischemia, cardiac conduction defects, and irregular cardiac rhythm [(5)]. Heart rate variability (HRV) is a non-invasive technique that describes the oscillations between successive ECG R-R intervals by assessing autonomic nervous system modulation on the cardiac sinus node. With the exception of specialist equipment, these variations are unnoticeable, ECG Holter monitoring is the gold standard. In order to assess cardiovascular risk and screen for the development of both acute and chronic heart disorders, HRV is regarded as an independent biomarker. A lower HRV is a result of disease or stress, whereas an enhanced HRV is associated with rest, exercise, and a full recovery [(6)]. Thus, this research aimed to study the electrocardiographic abnormalities and Holter findings in children with predialytic CKD.

PATIENTS AND METHODS
This cross-sectional study was conducted at Nephrology and Arrhythmia Clinic, Sohag University Hospitals, Egypt. Total coverage of all predialytic CKD children attending the clinic every Monday from 1st of November, 2022 to 30th November, 2023 and the sample size was fifty cases.

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Inclusion criteria: Age 1 to 15 year with predialytic CKD.

Exclusion criteria: Age > 15 years, cases on frequent dialysis, children with known CKD or known arrhythmia, and patients on probable medication impacting ECG readings such as B-blockers, antipsychotics, and antidepressants.

Data were collected from the studied cases through personal interviews with their parents or care givers. Then, anthropometric measures and laboratory investigations were assessed. Following a brief explanation of the purpose of the study and their acceptance data were collected in the form of five sections:

First section included detailed history taking (name, age, sex, residence, parent consanguinity and family history for similar condition), **second section** included clinical examination (anthropometric measurements and vital signs) and **third section** involved laboratory tests [complete blood count, serum creatinine, 25 hydroxycholecalciferol (Vitamin D), parathormone, urine analysis, albumin\creatinine ratio, venous blood gases, electrolytes that included serum potassium, sodium, phosphorus and ionized calcium and assessment of GFR using original Schawrtz (OS): eGFR = k x height (cm) /S Cr (mg), with k = 0.45 for full-term infants, 0.33 for preterm infants, 0.55 for children over 12 months, and 0.7 in teenage boys (females continue at 0.55 beyond age 13 years) [(7)]. **Forth section** included ECG (Fukuda Denshi CardiMax ECG device model FCP-7101, French). After the patients took a 10-minute break in a quiet room while lying down, all twelve ECG leads were recorded at the same time using a paper speed of 25 mm/s and a voltage of 10 mm/mV. The electrocardiograms were evaluated using descriptive reports to determine the following variables: P-wave amplitudes greater than 3 mm suggest right atrial enlargement, while wide P-waves imply left atrial enlargement. Combined atrial hypertrophy if tall and broad, PR interval, QRS duration, using Bazett's approach, the QT interval was modified to account for heart rate, unusually broad Q waves (more than 0.2 seconds) or abnormally deep Q waves (more than 5 mm). Each ECG paper was interpreted using particular centile charts for normal values of ECG waves and intervals based on age [(8)]. **Fifth section** involved children with predialytic CKD who were subjected all to 24 hours Holter monitoring (Mortara 2016 H3+, software: Mortara Company, America). The minimum, mean, and maximum heart rates, as well as the rhythms and corrected QT, were examined. Time domain parameters of heart rate variability, such as standard deviation of all R-R intervals (SDNN), standard deviation of the average of R-R intervals in all five-minute segments of the entire recording HRV Triangular Index, standard deviation of the 5 minute average NN intervals (SDANN), root mean squares differences between adjacent R-R intervals (RMSSD), and percentage of differences between adjacent R-R intervals that are greater than 50 milliseconds (pNN50). All Holter recorders were then evaluated. The analysis system employed a feature extraction approach to group individual QRS complexes based on their characteristics, as well as technician interaction in arrhythmia analysis, which is supplemented by visual superimposition to adjust for artifacts and errors.

Classification of CKD stages:

The following categorization of chronic renal illness according to stage was suggested by the Kidney Disease Outcomes Quality Initiative (KDOQI) [(9)]:

- Stage 1 disease is defined by a GFR normal > 90 ml/min per 1.73 m^2 and persistent albuminuria.
- Stage 2 disease is defined by a GFR of 60-89 ml\min per 1.73 m^2 and persistent albuminuria.
- Stage 3 disease is defined by a GFR of 30-59 ml\min per 1.73 m^2.
- Stage 4 disease is defined by a GFR of 15-29 ml\min per 1.73 m^2.
- Stage 5 disease is defined by a GFR of less than 15 ml\min or end stage renal disease.

Ethical considerations: The Ethical Committee of the Medical School of Sohag University gave its stamp of approval (Soh-Med-23-01-12) and every one of the patients' caretakers signed an informed permission form. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

The data were analyzed using STATA version 17.0 (Stata Statistical Software: Release 17.0 College Station, TX: StataCorp LP). The Kolmogorov-Smirnov test was utilized to determine if the variables have normal distributions. The mean ± SD, median, and range were the quantitative data's representations. In the data analysis, the means of the two and three groups were compared using two student t-tests and an ANOVA with a Bonferroni post hoc test respectively. We utilized the Kruskall-Wallis test for comparing three or more groups. In situations where the data did not follow a normal distribution, the Mann-Whitney test was used to compare two groups. Two tests were used to compare numerical and percentage-based qualitative data: the Fisher exact test and the X^2-test. Significance was defined as a p-value ≤ 0.05 or less.

RESULTS

The study included 50 predialysis CKD children, the mean age was 7.86 ± 4.19 years with 56% males. The mean weight was 22.43 ± 10.99 kg. Height showed a mean of 107.69 ± 25.36 cm. The mean Systolic blood pressure was 107.6 ± 15.88 mmHg. As regards CKD etiology the most common cause was congenital anomalies of the kidneys and urinary tracts (62%). Moreover, assessment of CKD stages showed that 50.00% had stage 3 CKD, 32.00% had stage 4 CKD and 18.00% had stage 5 predialytic CKD (Table 1).

Table (1): Basic characteristics of studied population

Variable	
Age /years Mean ± SD	7.86±4.19
Gender	
Female	22 (44.00%)
Male	28 (56.00%)
Weight/kg Mean ± SD	22.43±10.99
Systolic blood pressure	107.6±15.88
Height /cm Mean ± SD	107.69±25.36
Causes of CKD	
CAKUT	31 (62%)
Polycystic kidney disease	4 (8%)
FSGS and infantile nephrotic	14 (28%)
Vasculitis	1 (2%)
CKD stage	
Stage 3	25 (50%)
Stage 4	16 (32%)
Stage 5	9 (18%)

CAKUT: Congenital anomalies of the kidneys and urinary tracts.

As regards Hct and phosphorus, there was statistically significant difference between stage 3, stage 4 and stage 5. Also, regarding WBCs, Hb, anemia, platelets, sodium, potassium, calcium, parathormone hormone and 25 hydroxycholecalciferol, there was no statistically significant difference between stage 3, stage 4 and stage 5 (Table 2).

Table (2): Relation between Lab investigation of studied population and CKD

Variable	Stage 3 (N=25)	Stage 4 (N=16)	Stage 5 (N=9)	P value
WBCs (mcL) Mean ±SD	9.16 ± 2.21	10.18 ± 2.24	8.46 ± 1.47	0.85
Hb (g/dL) Mean ± SD	10.27 ± 1.67	9.61 ± 1.72	8.7 ± 1.8	0.07
Hct (%) Mean ± SD	30.89 ± 4.67	28.66 ± 5.9	25.1 ± 5.03	0.02
PLTs (mcL) Mean ± SD	290.68 ± 72.1	288.6 ± 70.5	236.4 ± 58.4	0.55
Anemia				
No	8 (32%)	2 (12.5%)	0 (0%)	0.8
Anemic	17 (68%)	14 (87.5%)	9 (100%)	
Parathormone (pg/mL) Mean ± SD	149.31 ± 13	346.8 ± 85.7	270.4 ± 65.8	0.2
25hydroxycholelerol Normal	8 (32%)	4 (25%)	2 (22.22%)	0.8
Low	17 (68%)	12 (75%)	7 (77.78%)	
Ca (mg/dL) Mean ± SD	8.67 ± 0.67	8.48 ± 1.64	8.13 ± 1.99	0.58
Potassium (mEq/L) Mean ± SD	3.9 ± 0.95	4.12 ± 0.79	4.49 ± 0.62	0.29
Sodium (mEq/L) Mean ± SD	135.49 ± 6.8	136.43 ± 5.59	133.71 ± 2.85	0.55
Phosphorus (mg/dl) Mean ± SD	4.58 ± 0.93	5.96 ± 1.37	5.63 ± 1.25	0.003

Figure (1) showed that 64% of patients had abnormal ECG findings, 22% had sinus tachycardia, 6% had high P wave amplitude, 10 % had wide P wave duration, 4% had prolonged PR interval, 2% had short PR interval, 6% had wide QRS duration, 30% had prolonged QTc interval, 2% had short QTc interval, 10% had left axis deviation, 4% had right axis deviation, 2% had upright T wave in V1, 2% had IRBBB in V1, which is normal in children and 2% had abnormal Q wave due to severe anemia (Figure 1).

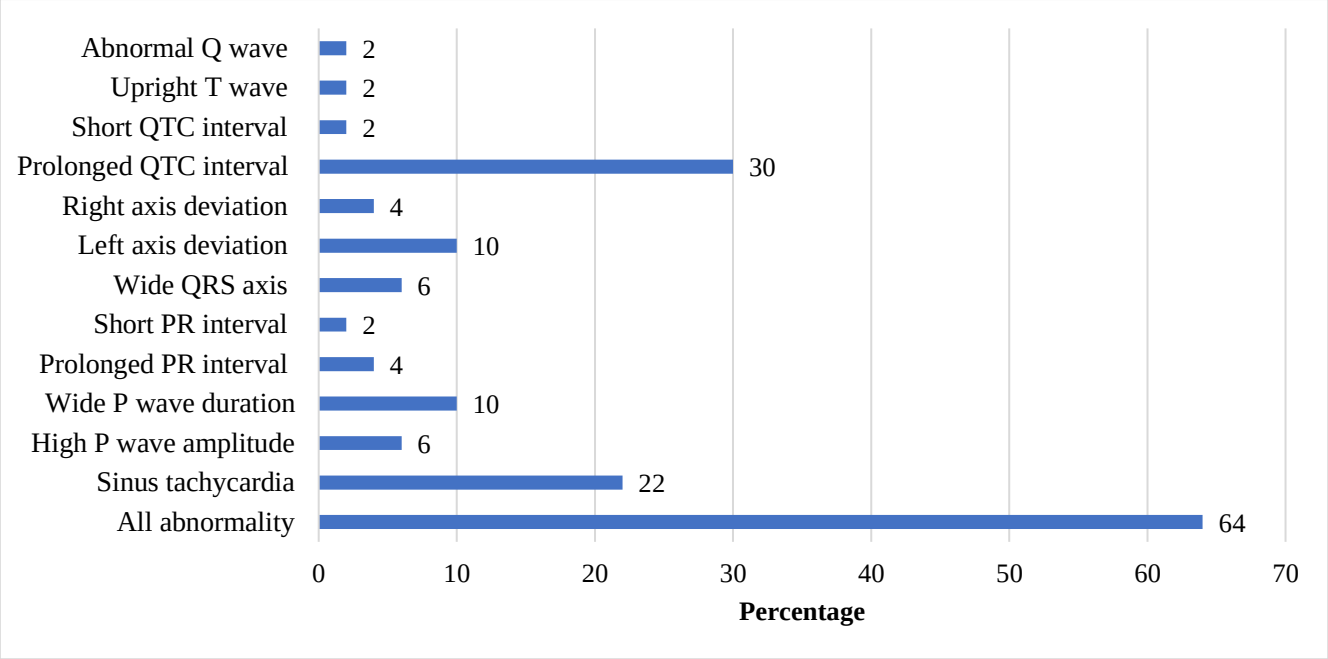

Fig. (1): Abnormal ECG finding in studied population.

There was statistically significant difference between different stages of CKD as regards Echocardiographic and ECG abnormality with left ventricular hypertrophy was the most common Echocardiographic abnormality. CKD stage 5 showed the highest ECG abnormality (100%), while there was no statistically significant difference between stage 3, stage 4 and stage 5 regarding heart rate, P wave amplitude, PR interval, QRS duration and QTc interval (Table 3).

Table (3): Relation between Echocardiography, ECG findings and CKD stages

Variable	Stage 3*N=25	Stage 4N=16	Stage 5N=9	P value
Echo finding				
Normal	21(84%)	13 (81.3%)	4 (44.4%)	P= 0.049
Abnormal	4 (16%)	3 (18.7%)	5 (55.56%)	
ECG finding				
Normal	12 (48%)	6 (37.5%)	0 (0%)	P= 0.04
Abnormal	13 (52%)	10 (62.5%)	9 (100%)	
ECG findings				
Heart rate				
Normal	20 (80%)	13 (81.3%)	6 (66.7%)	0.66
Sinus Tachycardia	5 (20%)	3 (18.7%)	3 (33.3%)	
P wave amplitude				
Normal	23 (92%)	16 (100%)	8 (88.9%)	0.45
High	2 (8%)	0 (0%)	1 (11.1%)	
PR interval				
Normal	23 (92%)	15 (93.8%)	9 (100%)	0.81
Prolonged	1 (4%)	1 (6.25%)	0 (0%)	
Short	1 (4%)	0 (0%)	0 (0%)	
QRS Duration				
Normal	23 (92%)	15 (93.8%)	9 (100%)	0.7
Wide	2 (8%)	1 (6.2%)	0 (0%)	
QTC interval				
Normal	18 (72%)	12 (75%)	4 (44.4%)	02
Prolonged	7 (28%)	4 (25%)	4 (44.4%)	
Short	0 (0%)	0 (0%)	1 (11.2%)	

Regarding relation between Holter and CKD stages, there was statistically significant difference between normal and abnormal Holter findings in stage 3, stage 4 and stage 5 as regards HR variability indices (there was statistically significant variation between CKD stages with CKD stage 5 participants having the lowest HR variability indices according to pNN50, RMSSD and there was no statistically significant difference between stage 3, stage 4 and stage 5 regarding mean heart rate, SDANN and Triangular Index) (Table 4).

Table (4): Relation between Holter and CKD stage among the studied participants

Variable	Stage 3* (N=25)	Stage 4 (N=16)	Stage 5 (N=9)	P value
Holter finding Normal Abnormal	 16 (64%) 9 (36%)	 12 (75%) 4 (25%)	 0 (0%) 9 (100%)	0.001
Mean heart rate (Mean ± SD)	100.16±16	106.56±13.7	108.67±21.3	0.30
PNN50 (Mean ± SD)	13.7 ± 10.8	5.8 ± 5.8	5.1 ± 8.1	0.02
RMSSD (Mean ± SD)	47.6 ± 19.4	36.9 ± 29.7	29 ± 20.9	0.01
SDNN (Mean ± SD)	51.8 ± 18.8	40.8 ± 14.9	34.1 ± 17.5	0.04
SDANN (Mean ± SD)	82.72 ± 40.36	74.69 ± 35.62	58.22 ± 26.27	0.29
TriangularIndex (Mean ± SD)	23.32 ± 7.14	19.43 ± 7.78	17.78 ± 7.03	0.24

There was highly statistically significant difference between patients with normal ECG and those with abnormal ECG regarding Ca^{++}, parathormone and sodium, while there was no statistically significant difference between both groups regarding to Hb, Hct, anemia, PLTs, phosphorus, potassium, sodium level, 25 hydroxycholecalciferol level (Table 5).

Table (5): Relation between ECG abnormalities and lab investigation

Variable	Normal ECG (N=18)	Abnormal ECG (N=32)	P value
Hb (g/dL) (Mean ± SD)	10.34 ± 1.63	9.46 ± 1.80	0.09
Hct (%) (Mean ± SD)	31.07 ± 4.65	28.04 ± 5.69	0.06
Anemia No Anemic	 6 (33.33%) 12 (66.67%)	 4 (12.50%) 28 (87.50%)	0.14
PLTs (mcL) (Mean ± SD)	263 ± 64.21	290 ± 70.82	0.86
Parathormone (pg/mL) (Mean ± SD)	170.04 ± 41.77	270.47 ± 66.45	0.02
25hydroxycholelerol Normal **Low**	 6 (33.33%) 12 (66.67%)	 8 (25%) 24 (75%)	0.5
Ca^{++} (mg/dL) Mean ± SD	9.06 ± 0.75	8.20 ± 1.47	0.03
Phosphorus (mg/dL) Mean ± SD	4.79 ± 1.15	5.44 ± 1.32	0.11
Potassium (mEq/L) Mean ± SD	4.22 ± 0.87	4.05 ± 0.86	0.5
Sodium (mEq/L) Mean ± SD	138.17 ± 3.66	133.95 ± 6.4	0.01

As shown in table (6), the only studied laboratory investigation, which had statically significant relationship was 25 hydroxycholecalciferol (Vit. D) deficiency with higher prevalence of vitamin D deficiency among patients with abnormal Holter changes.

Table (6): Relation between Holter abnormalities and lab investigation

Variable	**Normal Holter(N = 28)**	**Abnormal Holter (N = 22)**	**P Value**
WBCs (mcL) Mean ± SD	9.44±2.28	9.25±2.10	0.79
Hb (g/dL) Mean ± SD	9.95±1.69	9.56±1.89	0.45
Hct (%) Mean ± SD	30.15±4.92	27.84±6.01	0.14
MCV (μm^3) Mean ± SD	77.58±7.7	79.17±5.73	0.41
Anemia No Anemic	 6 (21.43%) 22 (78.57%)	 4 (18.18%) 18 (81.82%)	 1
PLTs (mcL) Mean ± SD	291.32±71.45	266.23±65.82	0.68
Parathormone (pg/mL) Mean ± SD	236.03±58.81	232.13±57.81	0.98
25hydroxycholelerol Normal Low	 11 (39.29%) 17 (60.71%)	 3 (13.64%) 19 (86.36%)	 0.045
Ca (mg/dL) Mean ± SD	8.59±1.12	8.41±1.55	0.65
Potassium (mEq/L) Mean ± SD	4.15±0.89	4.06±0.83	0.7
Sodium (mEq/L) Mean ± SD	136.9±4.85	133.65±6.68	0.052

According to PNN50, RMSSD and SDNN, there was significant negative correlation with CKD stage and serum creatinine. Concerning Triangular Index, there was significant negative correlation with CKD stage while there was significant positive correlation with Hb and Hct (Table 7).

Table (7): Correlation RR variability with lab investigation, blood pressure, CKD stages

Variable		PNN50	RMSSD	SDNN	SDANN	Triangular Index
Systolic blood pressure	r	-0.08	-0.10	0.01	0.04	0.10
	p	0.58	0.51	0.93	0.77	0.49
Diastolic blood pressure	r	-0.06	-0.10	-0.03	-0.04	0.05
	p	0.68	0.49	0.86	0.81	0.71
CKD stage	r	-0.42	-0.43	-0.38	-0.26	-0.28
	p	**0.002**	**0.002**	**0.006**	0.07	**0.047**
Hb (g/dL)	r	0.11	0.08	0.12	0.27	0.39
	p	0.44	0.59	0.39	0.06	**0.005**
Hct (%)	r	0.12	0.07	0.12	0.25	0.40
	p	0.39	0.62	0.40	0.09	**0.004**
PLTs (mcL)	r	-0.09	-0.12	-0.13	-0.18	-0.06
	p	0.54	0.42	0.39	0.20	0.67
Serum creatinine (mg/ dL)	r	-0.29	-0.35	-0.23	-0.13	0.06
	p	**0.04**	**0.01**	0.11	0.37	0.67
Albumin / creatinine (g/L)	r	-0.05	-0.11	-0.17	-0.21	-0.16
	p	0.74	0.45	0.23	0.15	0.27
Alkaline phosphate (mg/l)	r	-0.17	-0.18	-0.12	-0.11	-0.16
	p	0.24	0.21	0.40	0.43	0.27
Serum ferritin (ng/mL)	r	-0.11	-0.11	-0.09	0.04	0.09
	p	0.45	0.44	0.55	0.77	0.53
Ca (mg/dL)	r	0.10	-0.05	0.02	0.10	0.19
	p	0.48	0.73	0.89	0.51	0.18
Phosphorus (mg/dL)	r	-0.21	-0.07	-0.11	-0.09	-0.24
	p	0.15	0.61	0.46	0.54	0.08
Parathormone (pg/mL)	r	0.05	0.15	0.13	0.03	-0.09
	p	0.74	0.31	0.36	0.84	0.55
Potassium (mEq/L)	r	0.05	-0.005	-0.05	-0.08	-0.05
	p	0.73	0.97	0.74	0.56	0.73
Sodium (mEq/L)	r	0.18	0.14	0.18	0.05	0.24
	p	0.20	0.32	0.22	0.73	0.10
25hydroxycholelerol	r	0.03	-0.04	-0.08	-0.11	-0.009
	p	0.82	0.76	0.59	0.45	0.95
PH	r	0.06	0.11	0.09	0.07	-0.04
	p	0.69	0.43	0.52	0.61	0.80
HCO3	r	-0.12	-0.09	-0.11	-0.13	-0.21
	p	0.42	0.52	0.44	0.35	0.14

DISCUSSION

Premature mortality in children is associated with advanced CKD. As to the National Kidney Foundation (NKF), GFR below 60 mL/min/1.73 m^2 for more than three months, or kidney damage with structural or functional abnormalities, constitutes CKD. Congenital, acquired, hereditary, or metabolic causes may all contribute to pediatric CKD [10].

It seems that adaptive biochemical and hemodynamic processes are associated with cardiovascular changes that occur throughout the course of CKD. Alterations to the cardiovascular system tend to boost vascular and left ventricular function at first, but lower cardiorespiratory fitness and ventricular performance in the long run [11].

As regards relation between laboratory investigation of studied patients and CKD stages, the study results indicated that there was statistically insignificant difference between CKD stages and hemoglobin level. This study showed that anemic patients represented 80% of the studied cases and there was insignificant increase in percentage of anemic children with rise of stages of CKD. It was illustrated that 68% of children at stage 3 had anemia in comparison with 87.5% and 100% of children at stage 4 and stage 5 respectively. The study findings are substantially identical to those of **Atkinson *et al.*** [3] who found that anemia was frequent in 73% of stage 3 CKD patients, 87% in stage 4, and more than 93% in stage 5. **Avula *et al.*** [5] found that there was a statistically significant difference between the stages of CKD and hemoglobin levels. Inconsistent with the study findings, a cross-sectional descriptive research that was performed by **Esfandiar *et al.*** [6] who described that hemoglobin levels did not change significantly between children with moderate and severe chronic kidney disease.

As regards relation between electrolytes and venous blood gases and CKD stages, the current study showed that there was no difference between stages of CKD as regards sodium, potassium and Ca^{++} but phosphorus was higher among stage 4 and 5. The study findings are not in line with **Esfandiar *et al.*** [6] who discovered that patients with advanced CKD had lower serum calcium and sodium levels and significantly higher levels of phosphorus. Our results contradict these findings. Also the study findings do not align with a study that was conducted by **Ramadan *et al.*** [12] who reported that there was significant increase in sodium level among stage 3 and stage 4 in comparison with stage 5 (136.39 ± 4.6 and 119.99 ± 35.6). Also, potassium level was significantly increased among stage 5 in comparison with stage 3 and stage 4 (5.69 ± 1.7 and 4.23 ± 1.1). Moreover, there was statistically insignificant difference between Ca^{++} and phosphorus levels. The study's findings are consistent with those of **Avula *et al.*** [5] who reported no statistically significant difference between CKD stages and levels of sodium, potassium, and calcium, but a significant difference was observed between stages of CKD and levels of phosphorus.

ECG findings in this study showed that 64% of the studied cases had abnormal ECG in the form of sinus tachycardia, high P wave amplitude, abnormal PR interval, wide QRS duration, prolonged or short QTc interval. This agrees with the study that was done by **Dobre *et al.*** [13] who revealed that 452 (38.8%) had major, 346 (29.7%) had mild, and 367 (31.5%) did not have any ECG abnormalities. ECG abnormalities were in form of prolonged QT interval and short PR interval. **Kooman *et al.*** [14] postulated that the QRS complex and PR interval showed the majority of the ECG alterations linked to CKD. While, **Hage *et al.*** [15] found in a prospective cohort of patients with both HD and PD considered for kidney transplantation that QT prolongation was an independent predictor of all-cause death (HR = 1.008, 95% CI 1.001–1.014; P = 0.016). Also, Extended QRS interval was found to be an independent risk predictor for cardiovascular death by **Deo *et al.*** [16] in a prospective study of 3587 people with mostly early to moderate CKD [mean eGFR 50–60mL/min/1.73m^2, median follow-up 7.5years]. This finding held true even after controlling for LVMI and ejection fraction. Additionally, a longer PR interval was revealed to be an independent predictor of cardiovascular death (HR =1.62, 95%; CI 1.19–2.19) in this research. **Dobre *et al.*** [13] showed erratic relationships with mortality in CKD and ESKD, which might be accounted for by the effects of electrolytes and fluids on PR interval. Although the exact relationship between a longer PR interval and death is unknown, it could have something to do with atrial fibrillation or bradyarrhythmia-related mortality.

In this study, there were statistically significant difference between patients with ECG abnormalities compared to those with normal ECG as regards hypocalcemia, hyponatremia and hyperparathyroidism. Our findings are in agreement with the results of **Voroneanu and Covic** [17] who conducted the literature to determine the prevalence of ECG abnormalities in dialysis patients. They found that the altered structure and function of the heart due to uremia or cardiac ischemic disease, the compromised myocardium, the effects of HD on electrolyte balance (variations in potassium, ionized calcium, magnesium, or sodium levels), the body fluid composition, tissue hydration, or adrenergic activation are all linked to significant effects on the excitability of the heart cells and arrhythmias [17]. **Buemi *et al.*** [18] reported from Italian centers that studied patients on regular dialysis and showed a clear connection between low QTc and QTd, potassium content, and premature ventricular complexes. Also, our results are consistent with those of **Mulia *et al.*** [19], who indicated that aberrant levels of serum calcium, phosphorus, and potassium were found to be related

with extended QTc, which is thought to be highly prevalent in patients on HD.

As regards relation between 25 hydroxycholecalciferol and ECG of the studied participants, there was statistically insignificant difference between normal and abnormal ECG according to interpretation of 25 hydroxycholecalciferol. Our findings contradicted the findings of a research done by **Tuliani *et al.*** [(20)], which revealed that there was a statistically significant association between aberrant vitamin D levels and serious ECG abnormalities.

The study results showed that there was statistically insignificant difference between CKD stages and variation of QTc interval and the highest percentage was for normal QTc (72%, 75% and 44.44 %) for stage 3, stage 4 and stage 5 respectively. This is consistent with a research done by **Butani *et al.*** [(21)] who said that QTc prolongation is unusual in children with CRF in the absence of cardiac dilatation.

Studying Heart rate variability indices among CKD patients in our investigation indicated that there was statistically significant difference among CKD stages and SDNN, PNN50 and rMSSD. The lowest mean of SDNN, PNN50 and rMSSD was among cases of stage 5 (34.11±17.55, 5.078±8.12 and 29±20.89 respectively).

The current study showed that there was significant decrease in SDNN, SDANN and rMSSD among CKD stage 5 cases in comparison with other stages. **Chandra *et al.*** [(22)] reported that there was significant decrease in SDNN and SDANN among CKD stage 5 cases but there was insignificant decrease in rMSSD among CKD stage 4 cases in comparison with other stages. In agreement with a study conducted by **Avula *et al.*** [(5)] who illustrated that there was statistically significant difference between stages of CKD and SDNN and the lowest mean was among cases of stage 5 but the results weren't in line with ours as there was statistically insignificant difference among CKD stages according to PNN50 and rMSSD. The study findings are inconsistent with the findings of a cohort study that was carried out by **Thio *et al.*** [(23)] who showed that there was no significant association with change in eGFR regarding HR variability (rMSSD) but this study is in line with ours with presence of significant association between SDNN and lower baseline eGFR.

In this study there was a statistically significant difference between cases with normal Holter findings and those with abnormal Holter findings regarding level of 25-hydroxycholelerol. 86.36% of cases with abnormal holter findings were found to have low level of 25- hydroxycholecalciferol in comparison with 61.71% of cases with normal Holter. Our findings are supported by **Mann *et al.*** [(24)] who found that vitamin D deficiency is common in ESKD populations and is linked to worse cardiovascular outcomes. Vitamin D has also been shown to affect cardiac contractility and myocardial calcium homeostasis in humans in relation to cardiovascular pathophysiology. Moreover, our results are consistent with those of **Barsan *et al.*** [(25)] who reported a favorable correlation between vitamin D insufficiency and the development of atrial arrhythmias as well as notable alterations in ventricular repolarization, exemplified by a prolonged QTc interval.

The current study found a strong negative association between CKD stages and PNN50, RMSSD, and SDNN in terms of heart rate variability. The research's findings conflict with those of a study by **Wang *et al.*** [(26)], which demonstrated a negligible connection between rMSSD and PNN50 and a strong positive correlation between CKD stages and SDNN and SDANN.

The current study showed that there was insignificant correlation between 25 hydroxycholecalciferol with SDNN and rMSSD. A research by **Tak *et al.*** [(27)] that contradict our findings by showing a substantial connection between 25 (OH)D and SDNN but no indication of a significant link between 25(OH)D levels and RMSSD.

Limitations: Small sized sample of subjects, the cross-sectional nature of the study with absence of control group, and the cases were enrolled from a single center.

CONCLUSION

Study results revealed that there was an association between chronic kidney disease (CKD) and Cardiovascular disease (CVD) and its complications are a leading cause of death for persons with CKD. Statistical analysis revealed that individuals in the fifth stage of chronic renal sickness had the highest incidence of abnormalities observed by echocardiography, electrocardiography, and Holter monitoring. In relation to HRV, the levels of PNN50, rMSSD, and SDNN differed considerably between CKD stages, with the lowest values seen in patients in CKD stage 5. As CKD stages progressed, PNN50, rMSSD, SDNN, and the triangle index were somewhat negatively correlated.

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