



# Electrocardiographic measurements in children with pre-dialysis chronic kidney disease and undergoing kidney replacement therapy

Emre Leventoğlu<sup>1</sup> · Bahar Büyükkaragöz<sup>1</sup> · Furkan Çağrı Kavas<sup>2</sup> · Mert Can Holoğlu<sup>2</sup> · Akif Kavgacı<sup>3</sup> · Kibriya Fidan<sup>1</sup> · Aydın Dalgıç<sup>4</sup> · Sevcan A. Bakkaloğlu<sup>1</sup> · Fatma Sedef Tunaoğlu<sup>3</sup> · Oğuz Söylemezoğlu<sup>1</sup>

Received: 25 April 2023 / Revised: 3 August 2023 / Accepted: 7 August 2023 / Published online: 25 August 2023  
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## Abstract

Cardiovascular diseases are the main causes of morbidity in children with chronic kidney disease (CKD). Electrocardiography (ECG) can provide important information about cardiac functions and parameters associated with sudden cardiac death. This study aims to evaluate the potentially dangerous changes in CKD and kidney replacement therapies by ECG and to determine the value of ECG in predicting cardiovascular outcome compared with echocardiography. 101 patients with CKD were divided into subgroups according to treatment modalities as pre-dialysis CKD, hemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation (KTx). Differences in anthropometric measurements, laboratory results, blood pressures, ECG monitoring were compared within groups as well as with 40 healthy controls. Available echocardiographic findings were noted. In the patients, HD group had highest frequency of hypertension. ECG revealed prolonged QTc as more frequent (16.8% vs 0%,  $p=0.006$ ) and higher QTcD ( $56.7 \pm 6.5$  vs  $39.9 \pm 5.1$  ms,  $p=0.001$ ) in the patients compared to controls, especially in dialysis patients, whereas lowest values were in KTx subgroup. Left ventricular (LV) hypertrophy (LVH) was more frequent (47.1%) in HD compared to other CKD subgroups in ECG ( $p=0.052$ ). Echocardiography also showed LV mass index as highest in HD and lowest in KTx ( $121.4 \pm 55.7$  vs  $63.7 \pm 18.3$  g/m<sup>2</sup>,  $p=0.000$ ), with numerically highest LVH in HD (58.3%,  $p=0.063$ ).

**Conclusion:** ECG can be used to detect cardiovascular problems in patients with CKD, especially in HD. As ECG results were in line with echocardiography, patients with ECG abnormalities suggestive of LVH should be referred for echocardiographic assessment.

## What is Known:

- Cardiovascular diseases such as coronary artery disease, congestive heart failure, arrhythmias and sudden cardiac death are major causes of morbidity and mortality in chronic kidney disease.
- Electrocardiography has significant advantages in demonstrating cardiac functions in children because it is readily available, non-invasive and often non-experts can interpret the results.

## What is New:

- The heart rate is higher, QTc is longer and QTcD is higher in dialysis patients and the prolonged QTc is more frequent in patients with underlying glomerular diseases.
- Left ventricular hypertrophy is more common in HD patients and those with hypertension, hypercalcemia, anemia or glomerular etiology. The cardiovascular risky conditions are less frequent in the patients with kidney transplantation.

**Keywords** Electrocardiography · Echocardiography · Left ventricular hypertrophy · Chronic kidney disease · Dialysis · Kidney transplantation

## Introduction

Chronic kidney disease (CKD) refers to a condition of irreversible kidney damage and decreased kidney function associated with a progressive loss of kidney function over time [1]. The prevalence of CKD in children is 32.2 per million

Communicated by Peter de Winter

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age-related population in Europe [2]. However, it is probably underestimated because the early stages of CKD are often asymptomatic and lead to an underdiagnosis [3].

Follow-up for CKD includes preventing or slowing the progression of kidney disease, preventing or treating complications (such as mineral and bone disease, anemia, growth failure and cardiovascular diseases), and preparing for kidney replacement therapy (KRT) [4]. In children with kidney failure, KRT options include peritoneal dialysis (PD), hemodialysis (HD) and kidney transplantation (KTx) [5].

Cardiovascular diseases such as coronary artery disease, congestive heart failure, arrhythmias and sudden cardiac death are major causes of morbidity and mortality in CKD. Cardiovascular disease risk markedly increases parallel to the increase in the CKD stage, especially in patients with CKD stage 3 and beyond [6]. Cardiovascular risk is 20 times greater than general population and mortality in patients on dialysis is up to 10 times that of healthy controls [7, 8].

Electrocardiography (ECG) has significant advantages in demonstrating cardiac functions [9]. Arrhythmias including atrioventricular block, atrial or ventricular tachyarrhythmias; left/right bundle branch block and axis deviations, ST-segment deviation, T-wave inversion, pathologic Q-waves and right/left atrial enlargement can be determined with ECG [10]. Besides, ECG can provide important information about prolonged corrected QT (QTc) interval and increased QTc dispersion (QTcD) and left ventricular hypertrophy (LVH); the parameters which are known to be associated with sudden cardiac death [7, 11]. However, the efficacy or prognostic value of these ECG markers in children with CKD on determining cardiac abnormalities is of debate. Therefore, the aim of this study is to evaluate the presence and nature of potentially dangerous changes of cardiac conduction and repolarization via the 12-leads surface ECG and determine its value in predicting cardiovascular outcome when compared with echocardiographic findings during the course of CKD and in different forms of KRTs.

## Material and methods

### Design and selection of study subjects

This is a retrospective cohort study conducted on children with CKD with regular follow-up in a tertiary pediatric nephrology clinic in a single university hospital. All included subjects were aged 6 to 18 years.

Twelve-leads surface ECG monitoring was performed in 101 children with CKD who were clinically stable, and the patients were divided into four groups according to the mode of treatment: conservative therapy (i.e., pre-dialysis CKD), maintenance HD and continuous ambulatory PD (CAPD) and those with a successful KTx. Patients were

also subdivided into five groups according to the primary etiology: congenital anomalies of the kidney and urinary tract (CAKUT), glomerular diseases, kidney stones, CKD secondary to systemic diseases and unknown causes. Use of angiotensin converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARBs) were questioned in all participants. The control group consisted of 40 healthy age- and sex-matched children without cardiac disease. Exclusion criteria included the presence of amyloidosis, congenital heart disease and previous cardiac surgery, diabetes mellitus, thyroid gland dysfunction, atrial fibrillation, bundle branch block, and administration of antiarrhythmic drugs that might affect the QT interval.

Patients in the HD group underwent pre-HD session ECG monitoring on a day of dialysis. They were dialyzed routinely three times per week for an average of four hours. Patients on CAPD generally had four to five exchanges a day with a filling volume of 1200–1400 ml/m<sup>2</sup> per exchange with 1.36 dialysate. The KTx group consisted of patients who have undergone living-related or cadaveric transplants and continued their follow-up and treatment at the same center regularly.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Medical Ethics Committee.

### Data collection and assessment of laboratory parameters

Anthropometric measurements, including body weight, height, and blood pressure (BP) values, and laboratory results (hemoglobin (Hb), serum biochemistry including serum creatinine, sodium (Na), potassium (K), adjusted total calcium (Ca), phosphorus (P), magnesium (Mg), and blood gas analysis including pH and bicarbonate (HCO<sub>3</sub>) of the patients measured on the day of the ECG were recorded from the patient files.

Height-age and weight-age z scores were calculated by using data from Neyzi et al. [12, 13]. Children were categorized as severely underweight, moderately underweight, mildly underweight and overweight according to weight z scores and severely stunted, moderately stunted and mildly stunted according to height z scores [14]. Body mass index (BMI) was calculated using the weight/height<sup>2</sup> (kg/m<sup>2</sup>) formula and BMI-age z score was determined by using growth charts [15, 16]. According to BMI-age z scores, children were categorized as underweight, risk of overweight, overweight, and obese [17].

BP was measured using a manual auscultatory device. BP measurements were made from the right arm using an appropriate cuff size after 3–5 min of rest. We assured that all the

measurements were performed by the same fellow pediatric nephrologist in each control of the patients. The diagnosis and classification of hypertension was based on ‘Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents, 2017’ [18].

Anemia was diagnosed with an Hb value below 2.5th percentile according to age and sex [19]. The estimated glomerular filtration rate (eGFR) was calculated using the modified Schwartz formula (20). The eGFR of 90–120 ml/min/1.73 m<sup>2</sup> was defined as normal [21].

### ECG analysis

Twelve-lead ECG were recorded with a three-channel electrocardiographic recorder (Hewlett Pac- 3. Results kard, model 4745 A; Hewlett Packard, Camas, WA, USA) at a paper speed of 25 mm/s. The tracings were coded and analyzed by one of the authors who was blinded to the clinical data of the patients. All data obtained were confirmed by the pediatric cardiologist. The heart rate is calculated by dividing the number of large boxes between two consecutive R waves by 300. A normal resting heart rate is 60 to 100 beats per minute (bpm) for  $\geq 10$  years old, 60 to 140 bpm for 6–10 years old [22]. The PR interval, indicating atrial depolarization, is measured from the beginning of the upslope of the P wave to the beginning of the QRS wave. This measurement should be 0.12–0.20 s. The width of the QRS from the beginning of the Q wave to the end of the S wave represents ventricular depolarization and its duration should be less than 0.12 s. The QT interval is the time from the beginning of the QRS complex to the end of the T wave, resulting from ventricular repolarization. The normal QT interval is between 400 to 440 ms (ms) [23]. The QT was corrected for heart rate using Bazett’s formula [24]. The QTc interval was considered normal if it was  $< 440$  ms [25]. The QTcD was obtained by subtracting the minimum QTc from the maximum QTc. The normal range of QTcD has been determined as 10–70 ms [26, 27]. LVH was determined using Cornell voltage criteria, the method considered to be the most accurate (the specificity of 90% with a sensitivity of 20% to 40%) on ECG. The sex-specific Cornell voltage criteria was computed as the amplitude of R in aVL plus the amplitude of S or QS complex in V3 (RaVL + SV3) with a cutoff of  $> 2.8$  mV in males and  $> 2.0$  mV in females [28]. If an echocardiography evaluation was performed simultaneously with the ECG evaluation in the patient group, measurements of left ventricular end-diastolic diameter (LVEDD), posterior wall thickness (PWT) and diastolic interventricular septal thickness (IVST) were noted. Left ventricular mass (LVM) was calculated according to the formula by Devereux:  $LVM (g) = 0.8 \{ 1.04 [(LVEDD + PWT + IVST)^3 - (LVEDD)^3] + 0.6 \}$  [29]. The LVM index (LVMI) ( $g/m^2$ ) is calculated as the LVM

divided by the body surface area ( $m^2$ )  $[(4 \times \text{Weight (kg)} + 7) / (90 + \text{Weight (kg)})]$  [30]. LVH was defined as LVMI exceeding the 95th percentile for sex and age [31].

### Statistical analysis

In the presentation of descriptive statistics; the data obtained by measurement were expressed as mean  $\pm$  standard deviation (SD) and categorical data as number (percentage). Cross-table analyzes and Fisher’s exact Chi-square tests were used to compare the qualitative characteristics of the groups. Shapiro Wilks test was used to determine the normal distribution of numerical measurements in groups. Two groups were compared with t-test in independent groups and Mann–Whitney U test for those who did not show normal distribution. IBM SPSS Statistics version 22 package program was used for all statistical analyzes. Significance level of  $p < 0.05$  was taken.

## Results

### Demographic and anthropometric characteristics of the study population

The study included 101 patients with pre-dialysis CKD ( $n = 39$ ) and those undergoing KRT [PD ( $n = 21$ ), HD ( $n = 17$ ) and KTx ( $n = 24$ )] and 40 healthy controls. Majority of the participants were boys (62.4%,  $n = 63$ ) in the patient group. The sex distribution and mean age was similar in the patient and the control groups ( $p = 0.794$  and  $p = 0.798$ , respectively). In the subgroup analysis, although not statistically significant, KTx patients were older than the other patients, while the PD group was the youngest ( $p = 0.068$ ).

Mean dialysis duration was longest in PD and shortest in KTx patients prior to transplantation [2 (8.3%) patients had preemptive transplant, 15 (62.5%) HD, 7 (29.1%) PD] without statistical significance ( $p = 0.377$ ). The post-transplant period was  $39 \pm 24.1$  months in KTx patients.

Majority of the patients (61.4%) had CAKUT as the primary CKD etiology followed by glomerular pathologies (19.8%). Most common primary diagnosis was glomerular diseases in HD patients, and CAKUT in PD and pre-dialysis CKD patients. In addition, in KTx patients, the frequency of CAKUT was approximately 3 times higher than glomerular disease ( $p = 0.000$ ).

Mean weight and height z scores were significantly lower in the patients compared to the controls ( $p = 0.001$  and  $p = 0.000$ , respectively). In the subgroup analysis of the patients, weight, height, and BMI z scores were significantly lower in dialysis patients, with the lowest in HD group, and the highest in KTx group ( $p = 0.000$ ,  $p = 0.000$ , and  $p = 0.025$ , respectively).

The frequency of severe and moderate underweightness were higher in the patient group ( $n=32$ , 31.6%) than in the healthy controls ( $n=3$ , 7.5%) ( $p=0.000$ ). Besides, although none of the patient group had obesity, 5% of the controls consisted of obese subjects. More than half of the patients were stunted, whereas short stature was also observed in a quarter of the controls ( $p=0.003$ ). In sub-group analysis, underweightness and short stature were more prominent in HD and PD patients, and at the lowest rate in KTx ( $p=0.000$  and  $p=0.001$ , respectively).

Demographic and anthropometric characteristics of the study population are shown in Table 1.

### Evaluation of blood pressure in the study population

When compared in terms of office BP measurements, mean SBP z score was significantly higher in the patient group than in healthy controls ( $p=0.000$ ). In the sub-group analysis, the mean SBP z score was highest in the HD group, and lowest in the PD group ( $p=0.000$ ). Although there was no significant difference in terms of DBP z scores in our study, mean DBP z score was numerically higher in the patient group than in healthy controls ( $p=0.093$ ). In addition, mean DBP z score was at the highest value in the HD group ( $p=0.071$ , Table 1).

The patients had a lower frequency of having normal BP than healthy controls (66.3% vs 87.5%,  $p=0.042$ ). In the subgroup analysis, elevated BP or hypertension was observed in approximately half of the patients with HD, whereas it was present in only around one fourth of the patients with PD and KTx ( $p=0.000$ ) (Table 1).

The ACEi and/or ARBs were used in 27.7% of patients. The frequency of using at least one of these drugs was highest in the HD group and lowest in the KTx group ( $p=0.000$ ) (Table 1).

### Laboratory data of the study group

The mean Hb value was significantly lower and frequency of anemia was approximately 4 times higher in the patients compared to the control subjects ( $p=0.000$  and  $p=0.005$ , respectively). In sub-group analysis, the lowest mean Hb value was in dialysis patients, especially in those with HD ( $p=0.002$ ). Besides, anemia frequency was highest in dialysis patients ( $p=0.005$ ). Mean serum creatinine was higher and eGFR was lower in the patients compared with healthy controls, as expected ( $p=0.000$ , for both). Mean serum potassium and phosphorus values were higher and calcium values were also lower in the patients ( $p=0.032$ ,  $p=0.022$ , and  $p=0.000$ , respectively). In sub-group analysis, mean serum creatinine, potassium, and phosphorus were higher and mean serum calcium level was lower in dialysis patients ( $p=0.000$ , for all parameters). In addition, mean serum

magnesium level was lower in KTx patients compared to other groups ( $p=0.001$ ).

There were no significant differences between the patients and healthy controls in terms of hyponatremia or hypernatremia ( $p=0.658$ ). However, the frequency of hyperkalemia and hypocalcemia was higher in PD, HD and pre-dialysis CKD patients ( $p=0.013$  and  $p=0.000$ , respectively); and hyperphosphatemia was higher in HD, PD and pre-dialysis CKD patients in descending order ( $p=0.000$ ). All the controls had normal magnesium levels, but approximately one third of the patient group had magnesium levels outside the normal reference ranges. Frequency of hypomagnesemia was highest in the KTx group whereas hypermagnesemia frequency was highest in the PD group ( $p=0.000$ ). Metabolic acidosis was present in 18.8% of the patients, with a significantly higher ratio in dialysis patients than the other CKD subgroups ( $p=0.000$ ).

Laboratory data of the study population are shown in Table 2.

### ECG analysis of the study population

Mean heart rate was higher in the patients compared to the controls ( $p=0.004$ ). Mean PR interval was shorter in the patients ( $p=0.001$ ). Mean QTc was longer, and QTcD was higher significantly in the patient group ( $p=0.000$  and  $p=0.001$ , respectively). A total of 17 patients (16.8%) had prolonged OTc compared to none in the healthy control group ( $p=0.006$ ). LVH was also seen more frequently in the patients than the controls (21.8% vs 15%) but without statistically significant difference ( $p=0.363$ ).

In sub-group analysis, mean heart rate was highest in dialysis patients and lowest in KTx patients ( $p=0.014$ ). Mean QTc was longer, and QTcD was significantly higher in dialysis patients while lowest values were detected in KTx patients in terms of these two parameters ( $p=0.005$  and  $p=0.004$ , respectively). The prolonged OTc frequency was significantly greater in the dialysis subgroup (especially the PD patients,  $p=0.004$ ). Although LVH was detected in almost half of HD patients (47.1%), the difference in terms of LVH frequency between CKD subgroups was only in the range of borderline statistical significance ( $p=0.052$ ). The ECG findings in the study cohort are shown in Table 3.

Prolonged QTc was observed more frequently in patients followed up for glomerular diseases when compared with those with a primary diagnosis of CAKUT (35% vs 16.1%,  $p=0.002$ ). Furthermore, the frequency of the prolonged QTc was higher in patients with hyperkalemia, hypermagnesemia or hyperphosphatemia ( $p=0.028$ ,  $p=0.000$  and  $p=0.001$ , respectively). In addition, this rate was three times higher in patients with metabolic acidosis than in patients without acidosis (36.8% vs 12.2%,  $p=0.000$ ). Although not statistically significant, the frequency of prolonged QTc was numerically

**Table 1** Demographic and anthropometric characteristics of the study population

Demographic features	Sub-group analysis																											
	General analysis				Patient group (n = 101)				Controls (n = 40)				Pre-dialysis CKD (n = 39)				PD (n = 21)				HD (n = 17)				KTx (n = 24)			
	Mean±SD	Min - Max	n (%)	p value	Mean±SD	Min - Max	n (%)	p value	Mean±SD	Min - Max	n (%)	Mean±SD	Min - Max	n (%)	Mean±SD	Min - Max	n (%)	Mean±SD	Min - Max	n (%)	Mean±SD	Min - Max	n (%)	Mean±SD	Min - Max	n (%)	p value	
Age (years)	14.1 ± 3.5	6.2 – 18.0		0.798	13.7 ± 3.7	5.8 – 18.0		0.794	13.9 ± 2.6	4.7 – 18.0	24 (60%)	13.7 ± 3.7	5.8 – 18.0	22 (56.4)	13.1 ± 4.0	6.2 – 18.0	16 (76.2)	14.0 ± 3.6	4.3 – 18.0	9 (52.9)	15.8 ± 2.2	10.2 – 18.0	16 (66.7)	15.8 ± 2.2	10.2 – 18.0	16 (66.7)	0.064	
Male			63 (62.4)																									
<b>Primary diagnosis</b>																												
CAKUT			62 (61.4)	-																							0.000	
Glomerular diseases			20 (19.8)																								5 (20.8)	
Kidney stone			3 (3)																								2 (8.3)	
Secondary to systemic diseases			3 (3)																								0 (0)	
Unknown			13 (12.9)																								3 (12.5)	
<b>Dialysis duration (months)</b>			37.6 ± 23.1	6 – 96																							0.377	
<b>Post-transplantation duration (months)</b>																											-	
<b>Anthropometric measurements</b>																												
Weight z score	-1.10 ± 1.87	-5.24 – 2.56	20 (19.8)	0.001	0.02 ± 1.82	-3.05 – 3.38	2 (5)	0.000	0.02 ± 1.82	-3.05 – 3.38	2 (5)	-0.78 ± 1.64	-3.82 – 2.56	5 (12.8)	-1.72 ± 1.92	-5.24 – 1.12	7 (33.3)	-2.17 ± 2.06	-4.36 – 2.37	6 (35.3)	-0.31 ± 1.64	-4.56 – 1.79	2 (8.3)	-0.31 ± 1.64	-4.56 – 1.79	2 (8.3)	0.000	
Severely underweight																											0.000	
Moderately underweight			12 (11.9)																								0 (0)	
Mildly underweight			17 (16.8)																								7 (29.2)	
Normal			49 (48.5)																								15 (62.5)	
Overweight			3 (3)																								0 (0)	
Height z score	-1.35 ± 1.80	-6.16 – 3.21		0.000	0.25 ± 1.47	-2.91 – 2.27		0.000	0.25 ± 1.47	-2.91 – 2.27		-0.84 ± 1.73	-3.20 – 3.21		-1.97 ± 1.96	-6.16 – 0.87		-2.03 ± 1.92	-4.98 – 1.24		-1.16 ± 1.41	-5.16 – 0.56		-1.16 ± 1.41	-5.16 – 0.56		0.000	

**Table 1** (continued)

Demographic features	Sub-group analysis												p value	n (%)	Min - Max	n (%)	p value
	General analysis				Controls (n = 40)				Patient group (n = 101)								
	Mean ± SD	Min - Max	n (%)	p value	Mean ± SD	Min - Max	n (%)	p value	Mean ± SD	Min - Max	n (%)	p value					
Severely stunted	16 (15.8)	0 (0)	0.003	2 (5.1)	5 (23.8)	6 (35.3)	3 (12.5)	0.001									
Moderately stunted	21 (20.8)	4 (10)		10 (25.6)	4 (19)	5 (29.4)	2 (8.3)										
Mildly stunted	20 (19.8)	6 (15)		9 (23.1)	4 (19)	0 (0)	7 (29.2)										
Normal	44 (43.6)	30 (75)		18 (46.2)	8 (38.1)	6 (35.3)	12 (50.0)										
BMI ( $kg/m^2$ )	19.7 ± 4.8	12.5 - 29.3	0.860	20.1 ± 4.7	14.0 - 29.3	16.9 ± 4.2	12.5 - 25.9	17.5 ± 3.5	14.5 - 28.2	23.7 ± 4.2	15.8 - 29.3	0.001					
BMI z score	-0.46 ± 1.64	-3.69 - 2.39	0.300	-0.40 ± 1.64	-3.51 - 2.30	-0.82 ± 1.38	-2.97 - 1.22	-1.26 ± 1.89	-3.69 - 2.17	0.30 ± 1.40	-3.03 - 2.39	0.025					
Underweight	28 (27.7)	3 (7.5)	0.002	12 (30.8)	7 (33.3)	8 (47.1)	1 (4.2)					0.008					
Normal	49 (48.5)	25 (62.5)		17 (43.6)	12 (57.1)	6 (35.3)	14 (58.3)										
Obesity risk	19 (18.8)	4 (10)		9 (23.1)	2 (9.5)	2 (11.8)	6 (25)										
Overweight	5 (5)	6 (15)		1 (2.6)	0 (0)	1 (5.9)	3 (12.5)										
Obese	0 (0)	2 (5)		0 (0)	0 (0)	0 (0)	0 (0)										
ACEi and/or ARBs use	28 (27.7)	0 (0)	0.000	13 (33.3)	3 (14.3)	11 (64.7)	1 (4.2)					0.000					
<b>Blood pressure</b>																	
SBP z score	0.41 ± 1.13	-2.33 - 2.33	0.000	-0.36 ± 1.01	-1.64 - 1.75	0.10 ± 0.89	-1.41 - 1.64	1.04 ± 1.28	-1.64 - 2.33	0.32 ± 1.06	-1.88 - 2.05	0.000					
DBP z score	0.62 ± 0.96	-1.56 - 2.33	0.093	0.35 ± 0.55	-0.58 - 1.75	0.36 ± 0.78	-1.56 - 1.48	1.02 ± 1.18	-0.71 - 2.33	0.53 ± 0.89	-0.56 - 2.33	0.071					
Normal BP	67 (66.3)	35 (87.5)	0.042	24 (61.5)	16 (76.2)	9 (52.9)	18 (75)					0.000					
Elevated BP	5 (5)	1 (2.5)		0 (0)	2 (9.5)	0 (0)	3 (12.5)										
Stage 1 HT	15 (14.9)	4 (10)		11 (28.2)	3 (14.3)	1 (5.9)	0 (0)										
Stage 2 HT	14 (13.9)	0 (0)		4 (10.3)	0 (0)	7 (41.2)	3 (12.5)										

The p values in bold are statistically significant

CKD Chronic kidney disease, PD Peritoneal dialysis, HD Hemodialysis, KTx Kidney transplantation, CAKUT Congenital anomalies of kidney and urinary tract, BMI Body mass index, ACEi Angiotensin converting enzyme inhibitor, ARB Angiotensin receptor blocker, SBP Systolic blood pressure, DBP Diastolic blood pressure, HT Hypertension

**Table 2** Laboratory data of the study population

Laboratory analysis	General analysis										Sub-group analysis																			
	Patient group (n = 101)					Controls (n = 40)					Pre-dialysis CKD (n = 39)					PD (n = 21)					HD (n = 17)					KTx (n = 24)				
	Mean ± SD	Min - Max	n (%)	p value	Mean ± SD	Min - Max	n (%)	Mean ± SD	Min - Max	n (%)	Mean ± SD	Min - Max	n (%)	Mean ± SD	Min - Max	n (%)	Mean ± SD	Min - Max	n (%)	Mean ± SD	Min - Max	n (%)	Mean ± SD	Min - Max	n (%)	p value				
Hb	11.8 ± 2.6	6.4 - 16.3		<b>0.000</b>	14.2 ± 2.1	11.6 - 17.3		12.1 ± 1.9	9.4 - 13.5		11.9 ± 2.2	6.4 - 12.7		10.8 ± 2.0	8.9 - 13.3		12.6 ± 2.4	10.4 - 16.3												
Anemia			48 (47.5)	<b>0.005</b>			5 (12.5)			13 (33.3)				12 (57.1)		11 (64.7)														
Serum cre (mg/dL)	3.78 ± 2.97	0.82 - 11.9		<b>0.000</b>	0.59 ± 0.13	0.31 - 0.82		2.58 ± 1.62	0.82 - 6.96		6.52 ± 3.01	3.49 - 11.6		5.91 ± 2.53	2.0 - 11.9		1.84 ± 2.28	0.37 - 4.53												
eGFR (ml/min/1.73 m <sup>2</sup> )	27.4 ± 38.0	6.7 - 84.6		<b>0.000</b>	141.0 ± 25.5	112.0 - 160.7		30.5 ± 20.9	12.4 - 84.6		7.7 ± 5.0	10.2 - 15.1		8.0 ± 4.7	6.7 - 18.6		53.2 ± 64.6	14.4 - 133.2												
Na	139.0 ± 3.0	130 - 146		0.114	139.9 ± 2.4	134 - 143		139.6 ± 2.5	135 - 146		138.1 ± 3.9	130 - 144		138.6 ± 2.9	133 - 145		139.2 ± 3.0	133 - 144									0.148			
Normal			95 (94.1)	0.658			39 (97.5)		38 (97.4)				18 (85.7)		15 (88.2)												0.105			
Hyponatremia			5 (5)			1 (2.5)			0 (0)				3 (14.3)		2 (11.8)															
Hypernatremia			1 (1)			0 (0)			1 (2.6)				0 (0)		0 (0)															
K	4.44 ± 0.71	3.00 - 6.23		<b>0.032</b>	4.18 ± 0.33	3.59 - 4.90		4.35 ± 0.56	3.18 - 5.52		4.73 ± 0.92	3.00 - 6.14		4.72 ± 0.84	3.05 - 6.23		4.12 ± 0.42	3.37 - 4.79									<b>0.000</b>			
Normal			89 (88.1)	0.074			40 (100)		36 (92.3)				15 (71.4)		15 (88.2)												<b>0.013</b>			
Hypokalemia			5 (5)			0 (0)			2 (5.1)				2 (9.5)		0 (0)															
Hyperkalemia			7 (6.9)			0 (0)			1 (2.6)				4 (19)		2 (11.8)															
Ca	9.5 ± 0.7	6.8 - 10.8		<b>0.000</b>	10.1 ± 0.4	9.1 - 10.7		9.6 ± 0.4	8.4 - 10.8		9.2 ± 1.0	6.8 - 10.6		9.5 ± 0.9	7.1 - 10.7		9.7 ± 0.5	8.7 - 10.5									<b>0.000</b>			
Normal			83 (82.2)	<b>0.003</b>			27 (67.5)		35 (89.7)				15 (71.4)		13 (76.5)												<b>0.000</b>			
Hypocalcemia			7 (6.9)			0 (0)			1 (2.6)				5 (23.8)		3 (17.6)															
Hypercalcemia			11 (10.9)			13 (32.5)			3 (7.7)				1 (4.8)		1 (5.9)															
P	4.8 ± 1.4	2.8 - 8.3		<b>0.022</b>	4.3 ± 0.5	3.6 - 5.5		4.4 ± 1.0	2.5 - 6.6		5.5 ± 1.6	2.8 - 8.3		5.5 ± 1.5	3.1 - 7.9		4.3 ± 1.2	2.9 - 7.5									<b>0.000</b>			
Normal			48 (47.5)	<b>0.001</b>			31 (77.5)		22 (56.4)				5 (23.8)		3 (17.6)												<b>0.000</b>			
Hyperphosphatemia			53 (52.5)			9 (22.5)			17 (43.6)				16 (76.2)		14 (82.4)															
Mg	2.2 ± 0.4	1.3 - 4.0		0.583	2.1 ± 0.2	1.8 - 2.6		2.1 ± 0.3	1.3 - 3.1		2.4 ± 0.5	1.7 - 4.0		2.2 ± 0.3	1.6 - 2.9		1.9 ± 0.2	1.6 - 2.6									<b>0.001</b>			
Normal			70 (69.3)	<b>0.000</b>			40 (100)		31 (79.5)				11 (52.4)		12 (70.6)												<b>0.000</b>			
Hypomagnesemia			17 (16.8)			0 (0)			4 (10.3)				3 (14.3)		2 (11.8)															
Hyperagnesemia			14 (13.9)			0 (0)			4 (10.3)				7 (33.3)		3 (17.6)															
pH	7.37 ± 0.05	7.12 - 7.49		-				7.37 ± 0.03	7.26 - 7.45		7.36 ± 0.07	7.12 - 7.45		7.38 ± 0.04	7.33 - 7.49		7.38 ± 0.05	7.30 - 7.48									0.707			
HCO <sub>3</sub>	22.2 ± 3.2	11.0 - 31.8		-				22.3 ± 3.5	13.1 - 31.8		21.2 ± 4.3	11.0 - 27.4		22.6 ± 2.5	17.8 - 25.5		22.6 ± 2.0	19.1 - 26.1									0.435			
Normal			82 (81.2)	-		NA			35 (89.7)				15 (71.4)		12 (70.6)												<b>0.000</b>			
Metabolic acidosis			19 (18.8)			NA			4 (10.3)				6 (28.6)		5 (29.4)															

The p values in bold are statistically significant  
 CKD Chronic kidney disease, PD Peritoneal dialysis, HD Hemodialysis, KTx Kidney transplantation, Hb Hemoglobin, eGFR Estimated glomerular filtration rate, Na Sodium, K Potassium, Ca Calcium, P Phosphorus, Mg Magnesium, HCO<sub>3</sub> Bicarbonate, NA Not analyzed

**Table 3** The ECG findings of the study population

ECG parameters	General analysis												p value				
	Patient group (n = 101)				Controls (n = 40)				Sub-group analysis								
	Mean ± SD	Min - Max	n (%)		Mean ± SD	Min - Max	n (%)		Pre-dialysis CKD (n = 39)	PD (n = 21)	HD (n = 17)	KTx (n = 24)					
Pulse rate (/min)	93.4 ± 15.9	56 - 150		85.0 ± 14.0	53 - 115			94.1 ± 12.2	56 - 107	93.2 ± 15.6	78 - 136	97.8 ± 19.5	75 - 150	88.4 ± 18.2	65 - 125	<b>0.014</b>	
PR (s)	0.14 ± 0.02	0.08 - 0.20		0.15 ± 0.02	0.12 - 0.20			0.15 ± 0.02	0.10 - 0.20	0.13 ± 0.01	0.10 - 0.18	0.13 ± 0.01	0.12 - 0.16	0.13 ± 0.02	0.08 - 0.18	0.252	
QRS (s)	0.06 ± 0.01	0.04 - 0.12		0.06 ± 0.04	0.04 - 0.16			0.06 ± 0.01	0.04 - 0.08	0.08 ± 0.02	0.06 - 0.12	0.06 ± 0.01	0.04 - 0.08	0.06 ± 0.01	0.04 - 0.10	0.355	
QT (ms)	332.1 ± 34.7	240 - 400		322.5 ± 29.4	240 - 380			322.1 ± 33.0	280 - 400	342.9 ± 33.0	280 - 400	341.2 ± 42.1	240 - 400	332.5 ± 30.5	280 - 400	0.052	
QTc (ms)	410.9 ± 35.5	350 - 510		372.3 ± 32.2	300 - 420			404.1 ± 42.7	350 - 510	434.8 ± 24.4	400 - 480	415.4 ± 31.0	360 - 450	397.9 ± 22.2	350 - 440	<b>0.005</b>	
Normal		84 (83.2)			40 (100)				37 (94.9)		13 (61.9)		11 (64.7)		23 (95.8)	<b>0.000</b>	
Prolonged		17 (16.8)			0 (0)				2 (5.1)		8 (38.1)		6 (35.3)		1 (4.2)		
QTcD (ms)	41.9 ± 7.4	30 - 64		32.2 ± 3.7	24 - 48			48.9 ± 7.1	37 - 55	52.1 ± 8.4	42 - 64	51.9 ± 7.6	44 - 62	44.8 ± 6.4	30 - 52	<b>0.001</b>	
QTcD (ms)	56.7 ± 6.5	48 - 69		39.9 ± 5.1	36 - 50			56.7 ± 6.5	49 - 65	61.9 ± 8.3	54 - 68	62.7 ± 8.9	52 - 69	54.3 ± 5.8	48 - 61	<b>0.004</b>	
LVH (%)		22 (21.8)			6 (15)				6 (15.4)		3 (14.3)		8 (47.1)		5 (20.8)	0.052	
		Patient group (n = 66)							Pre-dialysis CKD (n = 25)								
		Mean ± SD	Min - Max	n (%)				Mean ± SD	Min - Max	n (%)		Mean ± SD	Min - Max	n (%)			
Echocardiography parameters		76.6 ± 37.9	34.1 - 185.4					66.5 ± 27.9	34.5 - 158.6			69.0 ± 21.3	34.1 - 121.2				
LVMI (g/m <sup>2</sup> )																	
LVH (%)		21 (31.8)						9 (36.0)			2 (12.5)		7 (58.3)		3 (23.1)		0.063

The p values in bold are statistically significant  
 CKD Chronic kidney disease, PD Peritoneal dialysis, HD Hemodialysis, KTx Kidney transplantation, QT Corrected QT, QTcD QT dispersion, QTcD QTc dispersion, LVH Left ventricular hypertrophy



higher in anemic patients compared to non-anemic ones (21.4% vs 14.2%,  $p=0.144$ ).

According to ECG analysis, the frequency of LVH was significantly higher in patients with glomerular disease than in patients with CAKUT (28.6% vs 8.1%,  $p=0.000$ ). Approximately half of the patients with stage 2 hypertension had LVH, whereas 19.6% of normotensive patients had LVH ( $p=0.066$ ). In addition, LVH was more common in patients with hypercalcemia than in the ones without hypercalcemia (35.7% vs 7.1%,  $p=0.009$ ) and in patients with anemia than those without anemia (47.9% vs 9.8%,  $p=0.006$ ).

When 66 patients with an available echocardiographic evaluation were investigated, mean LVMI was  $76.6 \pm 37.9$  g/m<sup>2</sup>. It was highest in HD and lowest in KTx patients ( $121.4 \pm 55.7$  vs  $63.7 \pm 18.3$  g/m<sup>2</sup>,  $p=0.000$ ). LVH was detected in 21 (31.8%) patients in general analysis. It was again numerically highest in HD patients (58.3%) ( $p=0.063$ ). The prevalence of LVH was 55.6% in glomerular disease and 20.9% in CAKUT ( $p=0.048$ ). In stage 2 HT, LVH was found in 61.5% of patients compared to 30% of normotensive patients ( $p=0.029$ ).

Cardiac evaluations of the study population are shown in Table 3.

## Discussion

In this retrospective study, in addition to impaired growth indices including lower weight and height z scores, findings compatible with CKD such as anemia, hypertension (especially with increased SBP z scores) and abnormalities in electrolytes including potassium, calcium and phosphorus were significant in the patient group despite presence of KRT modalities in the majority. Besides, ECG revealed higher mean heart rate, shorter PR interval, prolonged QTc and higher QTcD values in the patients compared to the controls. Glomerular diseases were more common in the HD group and CAKUT was the leading etiology in the other patients with CKD. Sub-group analysis showed the best growth parameters in KTx patients and worst in the HD group. Despite the considerably higher antihypertensive use, HD group had highest SBP z scores and frequency of hypertension. Hyperkalemia, hyperphosphatemia and hypocalcemia were more frequent in dialysis patients. The heart rate was higher, QTc was longer and QTcD was higher in dialysis patients. Prolonged QTc was more frequent in patients with underlying glomerular diseases. In addition, QTc was found to be longer in the states of electrolyte imbalance (hyperkalemia, hyperphosphatemia, hypermagnesemia) and metabolic acidosis. LVH was more common in HD patients and those with hypertension, hypercalcemia, anemia or glomerular etiology.

Children with CKD have a quite high prevalence of traditional (hypertension, dyslipidemia, obesity, etc.) and

uremia-related risk factors for cardiovascular disease [32]. From these, hypertension carries great importance as it affects more than 50% of pediatric CKD patients. Various factors including decreased nephron mass, increased sodium retention and extracellular volume expansion, sympathetic nervous system overactivity, activation of renin–angiotensin–aldosterone system and endothelial dysfunction can play role in hypertension pathogenesis [33]. Prolonged and uncontrolled hypertension is associated with the progression of CKD and the development of end-organ damage, including early cardiomyopathy and atherosclerosis [34]. In a recent study on adult patients with CKD, SBP was measured as significantly higher in dialysis patients than in pre-dialysis CKD [35]. In another study conducted on patients on chronic dialysis, CAKUT and glomerular diseases were compared, and hypertension was found more frequently in patients with underlying glomerular diseases [36]. In our study, office BP measurements revealed significantly higher SBP values in the patient subgroups (especially the HD patients) than in the controls. Although not statistically significant, we also obtained higher DBP values in HD patients. Therefore, we may conclude that patients in HD subgroup were under risk of cardiovascular disease in terms of BP control despite antihypertensive medications and interventions towards volume overload. On the other hand, despite being on dialysis, PD patients had the best values in terms of BP control among the CKD subgroups. We attributed this finding to the fact that majority of the patients in the PD group had a primary diagnosis of CAKUT and they still had sufficient urine output or even polyuria during PD treatment era.

Several clinical parameters and non-invasive tests such as ECG have been developed to determine the risk of cardiovascular complications in CKD [37, 38]. A higher heart rate is a surrogate marker of sympathetic nerve activity and is considered as one of the risk factors for heart failure and cardiovascular disease [23, 39]. A previous study demonstrated increased sympathetic activity in pediatric patients with CKD, which was correlated with the severity of kidney failure. In the same study, it was shown that sympathetic functional recovery occurred after KTx [40]. In another study, Converse et al. found a higher rate of sympathetic nerve discharge and consequently higher heart rate in adult patients on chronic dialysis [41]. There are also pediatric reports showing increased heart rate in patients with kidney failure [37]. In our study, we obtained higher heart rate on ECG analysis in the patient group compared to healthy controls. The highest values were noted in dialysis patients, especially in HD, whereas the heart rate was closest to healthy controls in KTx patients. Even with the heart rate alone, we can consider that our patients were at a higher cardiovascular risk and transplantation can contribute to a decrease in the adverse outcome.

The QTc interval, a measure of net ventricular myocardial depolarization and repolarization, is another important ECG

parameter for evaluating cardiovascular health. Prolongation of QT interval is associated with various components of the insulin resistance syndrome, age, body mass index, LVH, hypertension, CKD and in some studies the female gender [42]. Also, its prolongation is well described in association with electrolyte abnormalities including hypokalemia, hypocalcemia, and hypomagnesemia [43–45]. The prolongation of QT interval causes life-threatening cardiac arrhythmias including ventricular and atrial fibrillation and sudden cardiac death [46, 47]. QTcD is calculated as the difference between the maximum and the minimum QTc distances and its increase indicates heterogeneity in ventricular repolarization. Increased QT dispersion have been found in myocardial infarction, hypertrophic cardiomyopathy, hypertension, LVH, diabetes, chronic heart failure, mitral valve prolapses and genetically related long QT syndrome [48]. This parameter is also known to represent an increased risk of ventricular arrhythmias and sudden cardiac death like prolonged QTc interval [26, 49–51]. In a study conducted on pediatric dialysis patients, although there was no change in serum electrolyte levels, in more than half of the patients, a prolongation of the QT interval up to 40% was detected compared to the control group [45]. Similarly, Familoni et al. showed that QT and QTc intervals were prolonged, QTD and QTcD were increased in CKD patients, which worsened with dialysis treatment [51]. In another study by Özdemir et al., QTc was longer and QTcD was higher in children receiving HD compared to the healthy controls. In that study, it was mentioned that the patients may be at greater risk for sudden death due to the increase in QTcD reflecting the heterogeneous recovery of ventricular excitability [52]. In our study, QTc interval was longer and QTcD was higher in the patient group compared to the control subjects. The highest values for these two parameters were observed in dialysis patients. Although the mean serum potassium level was higher in our dialysis patients, which is unexpected to be associated with prolongation in QT interval, we believe that a combination several factors including the lower mean calcium level, presence of hypertension and CKD itself may have contributed to this outcome in dialysis patients.

Left ventricular hypertrophy remains the most reported cardiac complication in children with CKD [53, 54]. It is mainly secondary to increased BP and volume overload. Also, anemia, which causes a hyperdynamic state, and electrolyte disturbances such as hypocalcemia and hyperphosphatemia in the context of CKD may lead to LVH [54]. Matteucci et al. reported the prevalence of LVH as 35% in pediatric patients with stage 2 to 4 CKD and left ventricular mass was shown to be correlated with the degree of kidney dysfunction [50]. Similarly, LVH was found to be 70% in pediatric patients with CKD stage 5 [55]. On the other hand, a prospective study on pediatric CKD patients showed development of LVH in 32% of patients within two years even in the absence of progression

in the CKD stages [56]. Presence of LVH can be estimated via ECG analysis [23]. However, a previous study showed low sensitivity and low negative predictive value of ECG for detecting LVH in children. The authors recommended that echocardiographic examination should be applied to confirm the LVH in clinical practice [9]. On the other hand, a more recent report indicated a higher sensitivity and specificity of ECG for the diagnosis of LVH [28]. Although reports focusing on this topic are scarce, we believe that conflicting results in the literature can stem from the use of different methods in the evaluation of LVH via ECG. In our study, although not statistically significant, LVH was detected more frequently by ECG in the patient group compared to the controls (21.8% vs 15%). In the subgroup analysis, LVH was most prominent in HD patients (47.1%), with a borderline statistical significance. Taking into account the increased percentage of other risk factors associated with LVH in these subsets of patients such as hypertension, anemia, hypocalcemia, hyperphosphatemia, and glomerular disease frequency as a primary diagnosis, we may speculate that LVH detected on ECG reflects the reality. Fortunately, we were able to evaluate 66 patients by echocardiography concurrently. In our study, echocardiography showed highest mean LVMI in HD patients and LVH was proportionally more frequent in them. The frequency of LVH was significantly higher in glomerular disease than in CAKUT. In stage 2 HT, LVH was also significantly more frequent compared to normotensive patients. Therefore, as ECG analysis results were in line with echocardiography, we think that LVH detected on ECG should not be ignored and patients particularly with ECG abnormalities that are suggestive of LVH should be referred for echocardiographic assessment for definitive diagnosis.

Kidney transplantation improves several clinical parameters, including cardiac functions. For example, Souza et al. showed that left ventricular mass decreased in the first two years after transplantation [57]. Similarly, in another study, a significant regression of LVH was observed even within 6 months after KTx [58]. The results of our study showed that the frequency of LVH via both ECG and echocardiography in KTx patients was considerably lower than in HD patients but mildly higher than in PD patients. However, echocardiography demonstrated lowest LVMI values despite increased age in the KTx group. Therefore, we may conclude that a significant improvement has been achieved in terms of LVH after transplantation. In our study, it is noteworthy that. In addition, there was an improvement on growth parameters such as weight and height z scores and BMI, as well as ECG parameters such as heart rate, QTc interval and QTcD in KTx patients when compared to dialysis patients. With this data, it can be concluded that KTx has a significant positive effect on growth and cardiac functions, which can be easily demonstrated via ECG.

In conclusion, we believe that non-invasive tests such as BP measurement and ECG evaluation that can be easily

applied in every center can be used to detect cardiovascular problems in patients with CKD and KRT, especially in patients with HD, as our findings indicate highest cardiovascular risk in this group. By this way, it can be ensured that precautions can be taken for cardiovascular complications that may even result in sudden death. In addition, as the cardiovascular risky conditions were less frequent in our patients followed up with KTx, this result also highlights the vital importance and benefit of transplantation on the cardiac health.

**Authors' contributions** Emre Leventoğlu, Bahar Büyükkaragöz, Furkan Çağrı Kavas, Mert Can Holoğlu and Akif Kavgacı contributed to conception and design; contributed to acquisition, analysis, and interpretation; Emre Leventoğlu and Bahar Büyükkaragöz wrote the main manuscript text; Furkan Çağrı Kavas, Mert Can Holoğlu and Akif Kavgacı prepared the tables; Bahar Büyükkaragöz, Kibriya Fidan, Aydın Dalgıç, Sevcan A Bakkaloğlu and Fatma Sedef Tunaoğlu critically revised the manuscript; Sevcan A Bakkaloğlu, Fatma Sedef Tunaoğlu and Oğuz Söylemezoğlu gave final approval; All authors agree to be accountable for all aspects of work ensuring integrity and accuracy. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by and Akif Kavgacı. The first draft of the manuscript was written by Emre Leventoğlu. Kibriya Fidan, Aydın Dalgıç, Sevcan A Bakkaloğlu, Fatma Sedef Tunaoğlu and Oğuz Söylemezoğlu commented on previous versions of the manuscript and critically revised the manuscript. All authors read and approved the final manuscript.

**Data availability** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Medical Ethics Committee of Gazi University (file number 2022–1468).

**Consent to participate** Written informed consent was obtained from all participants and their parents. Our research was carried out in line in accordance with the standards.

**Conflict of interest** The authors have no conflicts of interest to disclose.

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## Authors and Affiliations

Emre Leventoğlu<sup>1</sup>  · Bahar Büyükkaragöz<sup>1</sup> · Furkan Çağrı Kavas<sup>2</sup> · Mert Can Holoğlu<sup>2</sup> · Akif Kavgacı<sup>3</sup> · Kibriya Fidan<sup>1</sup> · Aydın Dalgıç<sup>4</sup> · Sevcan A. Bakkaloğlu<sup>1</sup> · Fatma Sedef Tunaoğlu<sup>3</sup> · Oğuz Söylemezoğlu<sup>1</sup>

✉ Emre Leventoğlu  
dremrelevent@gmail.com

<sup>1</sup> Faculty of Medicine, Department of Pediatric Nephrology, Gazi University, Ankara, Turkey

<sup>2</sup> Faculty of Medicine, Department of Pediatrics, Gazi University, Ankara, Turkey

<sup>3</sup> Faculty of Medicine, Department of Pediatric Cardiology, Gazi University, Ankara, Turkey

<sup>4</sup> Faculty of Medicine, Department of Transplantation Surgery, Gazi University, Ankara, Turkey