http:// ijp.mums.ac.ir
Original Article (Pages: 16434-16448)

Clinical Signs and Causes of Chronic Kidney Disease in Pediatrics

Elham Zarifi [1], Simin Sadeghi-Bojd [2], *Alireza Teimouri [3]

[1] General Physician, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[2] Pediatric Nephrologist, Children and Adolescents Health research center, Research Institute of cellular and Molecular Science in Infectious Diseases , Zahedan University of Medical Science's, Zahedan, Iran.

[3] Demographer, Children and Adolescents Health research center, Research Institute of cellular and Molecular Science in Infectious Diseases , Zahedan University of Medical Science's, Zahedan, Iran.

Abstract

Background: Chronic kidney disease (CKD) is a worldwide medical condition with increasing frequency that impairs the quality of life of children. This study aimed to assess the clinical signs and causes of CKD in children in Zahedan, Iran.

Methods: This cross-sectional study was run on 489 children up to 20 years with stages of 3 to 5 CKDs, in Zahedan during 2010-2019. Informed written consent was obtained from the patients' parents. Data analysis was performed by SPSS 20 considering 0.05 as significant level.

Results: Amongst the clinical manifestations, edema (16.4%), (FTT) (13.5%), urinary symptoms (12.3%) and vomiting (11.5%) were more common and congenital structural anomalies (41.7%) were the most common cause of hospital admission. From among the studied children with CKD, 65.8% had stage 5, about 44.4% had conservative treatment and in total, 19.00% died. Most of the laboratory parameters were different in death and survival cases, for instance, Systolic and diastolic BP were higher in deaths when platelet blood was lower. Main causes of CKD (congenital structural anomalies, cystic/hereditary/congenital disease, glomerular diseases, Renal Tubular Disease, unknown origin and stone) had a significant association with gender ($X2=13.42$, $p=0.02$), treatments ($X2=70.77$, $p<0.001$), stage of CKD ($X2=40.31$, $p<0.001$) and survival ($X2=11.59$, $p=0.041$). Stages of CKD had a significant relation with treatment ($X2=118.18$, $p<0.001$), and survival ($X2=26.5$, $p<0.001$).

Conclusion: The causes of CKD were significantly associated with treatments, stage of CKD, and survival. Stages of CKD had significant associations with treatment and survival. Therefore, more attention to children with these signs is essential for early diagnosis and proper treatment.

Key Words: Causes, Chronic Kidney Diseases, Clinical Signs, Pediatrics.

* Please cite this article as: Zarifi E, Sadeghi-Bojd S, Teimouri A. Clinical Signs and Causes of Chronic Kidney Disease in Pediatrics. Int J Pediatr 2022; 10 (8):16434-16448. DOI: **10.22038/ijp.2022.65403.4934**

Corresponding Author:

Alireza Teimouri, Demographer, Children and Adolescents Health research center, Research Institute of cellular and Molecular Science in Infectious Diseases, Zahedan University of Medical Science's, Zahedan, Iran. Email: alirezateimouri260@gmail.com

Received date: May.07,2022; Accepted date:Aug.14,2022

1- INTRODUCTION

Chronic kidney disease (CKD) is a worldwide health problem that is increasing in prevalence and impairs the lives of children (1). Without any underlying reason, CKD is a clinical disorder that results in a slow loss of kidney function over a long period of time (2). The presence of kidney damage is known to occur due to a decrease in glomerular filtration rate (GFR) within 90 days (2.3). The reports of CKD in children focus on the end-stage renal disease (ESRD) requiring renal replacement therapy (RRT), in up to 9 per million children (4.5). The necessary screening avoids these problems so that patients at an earlier stage are likely to outnumber those who have had multiple ESRD visits (6) with the same pediatric predisposition. Therefore, the true effect of CKD in pediatrics is unclear in countries where health care assets are poorly allocated to RRT or where RRT is not accessible with high mortality due to 'IRC (4). It has been explained that the incidence of CKD is higher in boys due to the greater recurrence of renal intrinsic abnormalities and congenital abnormalities of the kidney and urinary tract (CAKUT) in this sexual orientation. (2). In Iran, the incidence of CKD in children decreased from 10.2 to 8.6% between 1996 and 2005 (7) with an annual incidence of stage 3-5 CKD of 14.5 parts per million (8). The main causes of CKD are proven by (CAKUT), Steroid Resistant Nephrotic Syndrome (SRNS) and kidney disease (9) while some causes like Wilms cancer, thrombosis, kidney stones, incurable diseases y and interstitial tissue are rarer (10). In this regard, the underlying cause of renal hypoplasia or posterior urethral valve certainly predominates in younger patients (4). Factors such as nephron reduction in infancy, low birth weight and low gestational age are now appearing to be important causes with the general hypothesis (2.11) being inaccessible due to lack of registries in world countries especially less developed countries (4). The clinical needs for renal failure in children and society's resistance to future development are normal but somehow more confusing about children (14), because of the short survival time and under-nutrition that have been observed in children with failure to thrive (FTT) around the world and in Iran (12,13). The developmental impairment increases as GFR decreases, despite a significant reduction in kidney function (14), which is a major cause of FTT in children (11) mainly due to malnutrition, metabolic acidosis, mineral and bone disorders, anemia, fluid and electrolyte disturbances and anomaly (15). Anyway, especially after infancy, developmental frustration is primarily due to a disruptive effect on the development of adult growth hormone (GH) digestion, the growth factor insulin-like (14-16). CKD is a stealthy disease; despite the fact that it is somewhat unusual in young people, it can be an overwhelming disease with long-lasting results. In fact, the mortality rate in children with ESRD treated with dialysis is 30 to 150 times higher than in healthy controls, and life expectancy is about 50 years less. Kidney transplantation is a treatment that improves the prognosis of children with ESRD (4). Regarding the second author's experience of the present study, the epidemiology and etiology of childhood CKD, early diagnosis, and identification of modifiable causes are important to make decision to choose an ideal treatment. It is necessary to be noted that the pediatric population of the present study, most of the children with CKD who referred to the pediatric nephrology clinic, had been suffering from inherited diseases due to parents' consanguineous marriages. This highlighted that social factors lead to kidney failure over time gradually due to underline diseases such as cystic/hereditary/congenital disease, renal

tubular disease, and late referral that lead to specific types of treatment (10). Considering the above-mentioned facts, the present study aimed to study clinical signs and causes of pediatric CKD in the city of Zahedan, located in the Southeast of Iran.

2- MATERIALS AND METHODS

2-1. Study design and setting

This cross-sectional study was run on 489 children aged less than 20 years with CKD stages of 3 to 5, who had referred to and admitted in the Ali Ebne Abi Talib Hospital, which is under the supervision of Zahedan University of Medical Sciences, Iran, during 2010-2019.

In this study the researcher referred to the medical record and assessed the profiles of the children with CKD and all children who had referred to the hospital entered the study after meeting the inclusion and exclusion criteria within the study duration.

All admitted children went under clinical examination and the information was recorded in a structured form, including the details of age, gender, anthropometry, admission disease category (neurological, respiratory, cardiovascular, gastrointestinal, etc.).

All the enrolled subjects received treatment according to the specific protocol and were followed until death or discharge from hospital.

The patients younger than 3 months and older than 20 years were excluded from the study. Stages 3 to 5 CKD were defined according stage 3a: GFR between 45-59 mL/min/1.73 m 2, stage 3b between 30-44 mL/min/1.73 m 2, stage 4 between 15-29 mL/min/1.73 m 2 and stage 5 less than 15 mL/min/1.73 m 2. Blood pressure higher than the 95th percentile plus 5 mmHg was considered as hypertension (10).

In order to simplify the assessment, patients were categorized into 6 groups regarding their etiologies for CKD, including: congenital structural anomalies of the kidney and urinary tract (CAKUT), congenital disease, and glomerular nephritis, renal tubular disorders, stone and unknown.

2-2. Data Analysis

For analyzing data, SPSS 18.0 (SPSS Inc., Chicago, Illinois, USA software) was implemented. Data grouping was summarized by frequencies and proportions, and the quantitative data represented with mean and standard deviations. Normality test was applied for the data distribution. For comparing the quantity variables in two groups, Mann-Whitney test was performed for the variables with free distribution and t-test for normal variables. Chi- square test was applied for assessing the association between two different categorical variables. P-value of 0.05 was considered as statistically significant.

3- RESULTS

Table 1 showed the results of the normality test with an illustration of free distribution for all the quantitative variables that caused non-parametric tests for analysis ($P<0.05$).

Most of the children aged higher than 10 years (44.6%), followed by the age group of 5-10 years (32.1%). Gender distribution was similar in boys (51.9%) and girls (48.1%).

The most frequent clinical manifestation included FTT (13.5%), edema (16.4%), lower urinary tract symptoms (12.3%), and vomiting (11.5%). Regarding the causal point of view on CKD, 41.7% were admitted due to congenital structural anomalies, 15.3% due to cystic/hereditary/congenital disease, and 24.1% due to glomerular diseases.

Table-1: Kolmogorov–Smirnov test (KS test) of normality on quantities variables in the study

Variables	N	Min	Max	Mean	SD	Skewness		Kurtosis		KS	P value
Age (Year)	489	0.3	20	9.01	4.98	-0.079	0.11	-0.977	0.22	0.078	<0.001
Weight	489	2	68	20.97	11.71	0.66	0.11	-0.109	0.22	0.102	<0.001
Height	489	43	162	109.05	26.49	-0.397	0.11	-0.637	0.22	0.088	<0.001
Systolic Blood Pressure	485	60	250	115.86	30.00	1.253	0.111	2.323	0.221	0.148	<0.001
Diastolic Blood Pressure	481	40	150	73.97	18.03	1.042	0.111	1.8	0.222	0.159	<0.001
White blood cell	477	1100	31000	8771.49	4402.88	1.733	0.112	3.832	0.223	0.152	<0.001
Hemoglobin (Hb)(mg/dl)	468	2.4	15	9.03	2.09	-0.213	0.113	-0.011	0.225	0.068	<0.001
platelet count (mcL)	404	15700	852000	265227.23	135145.54	1.249	0.121	2.614	0.242	0.096	<0.001
Erythrocyte Sedimentation Rate (mm/h)	214	0	145	58.27	34.83	0.454	0.166	-0.477	0.331	0.066	0.025
Blood urea nitrogen(mg/dl)	487	11	205	68.65	36.70	0.903	0.111	0.614	0.221	0.086	<0.001
Creatinine (mg/dl)	489	1	15.9	4.88	3.05	0.949	0.11	0.445	0.22	0.109	<0.001
Sodium (mEq/l)	483	109	164	138.44	6.14	-0.401	0.111	2.186	0.222	0.064	<0.001
Potassium (mEq/l)	485	2.2	58	4.68	2.61	17.639	0.111	359.703	0.221	0.239	<0.001
Calcium (mg/dl)	474	4.4	11	8.64	1.22	-0.606	0.112	0.239	0.224	0.091	<0.001
Phosphor (mg/dl)	462	1.4	13	5.55	1.73	0.713	0.114	0.834	0.227	0.113	<0.001
Alkaline phosphatase (mg/dl)	395	0.9	5475	793.90	562.74	2.495	0.123	13.524	0.245	0.12	<0.001
PH	452	6.28	9.23	7.25	0.16	3.536	0.115	50.803	0.229	0.123	<0.001
Carbon dioxide	451	2.3	24	13.89	4.50	-0.177	0.115	-0.685	0.229	0.072	<0.001
parathyroid hormone (mg/dl)	63	7.8	1013	300.06	251.85	0.987	0.302	0.499	0.595	0.13	0.01
Glomerular filtration rate	489	2.32	56.76	14.29	10.29	1.451	0.11	1.884	0.22	0.148	<0.001

Our children involved with the stages of 3, 4 and 5 such that most of the children including 322 patients (65.8%) were in stage 5, and about 116(23.7%) involved with the stage 4 and 51(10.4%) had stage 3 mostly in 3A (8.4%) compared with 3B (2.0%). The duration of the disease until the examination was another factor considered in the study; most of the children had 1-5 y illness duration with the frequency of 212 (43.4%). Children with illness duration >5 years, placed in the second rank with 187(38.2%). The majority of children had conservative treatment (44.4%), HD (25.6%) and PD (21.9%). In total, 40 (8.2%) patients were treated by TX. From 489 children about 19% died during the study (**Table 2**).

Table-2: Frequency distribution of qualitative variables of sex, clinical manifestation, main causes of CKD, stages of kidney disease, duration of illness, treatment, age groups and survival

Variables	options	Frequency	Percent	Variables	options	Frequency	Percent
Gender	Boys	254	51.9	stages of kidney disease	4	116	23.7
	Girls	235	48.1		5	322	65.8
Clinical Manifestation	Anemia	28	5.7		3A	41	8.4
	HTN	39	8		3B	10	2
	FTT	66	13.5	Duration of illness	<1y	90	18.4
	polyuria	20	4.1		1-5y	212	43.4
	Edema	80	16.4		>5y	187	38.2
	Vomiting	56	11.5	Treatment	conservative	217	44.4
	Respiratory symptom	44	9		PD	107	21.9
	Wasting	34	7		HD	125	25.6
	Urinary symptom	60	12.3		TX	40	8.2
	UTI	35	7.2				
	Seizure	23	4.7	Age Groups	<1	38	7.8
	Other	4	0.8		1_5	76	15.5
Main Causes of CKD	Congenital structural anomalies	204	41.7		5_10	157	32.1
	Cystic/hereditary/congenital disease	75	15.3		>10	218	44.6
	Glomerular diseases	118	24.1	Survival	Alive	396	81
	Renal Tubular Disease	40	8.2	-	Death	93	19
	Unknown origin	26	5.3	-	Total	489	100
	Stone	26	5.3	-	-	-	-

Table 3 presents a comparison in age, weight, height, blood measures' and urine tests between survived and died children. The results show that systolic and diastolic blood pressure, hemoglobin (Hb), platelet, blood urea nitrogen, creatinine, serum pH, carbon dioxide, glomerular filtration rate (GFR) were significantly different in survived children compared to the dyed cases. Systolic, diastolic blood pressure, blood urea nitrogen and creatinine were higher in died children ($p<0.001$) when Hb ($p<0.001$), platelet count ($p=0.002$), pH and carbon dioxide ($p<0.001$), glomerular filtration rate (GFR) were higher in survived children.

Table 4 demonstrates the association between main causes of CKD and gender, age, duration of illness, treatment, stages of kidney disease and survival. It is indicated that main causes of CKD had significant association with gender ($X2=13.42$, $p=0.02$), treatment ($X2=70.769$, p $p<0.001$), stages of kidney disease ($X2=40.309$, $p<0.001$) and survival ($X2=11.59$, $p=0.041$).

From 204 children with congenital structural anomalies, 124(60.8%) were boys, 80(39.2%) aged above 10 years, 90 (44.1%) had more than 5 years of duration in the illness, 105(51.5%) treated conservative, 138(67.6%) had stage 5 of kidney disease and 169 (82.8) survived. From 75 children with cystic/hereditary/congenital disease, 39 (52%) were boys, 33 (44.0%) aged above 10 years, 29 (38.7%) had a duration of more than 5 years in the illness, 30 (40%) treated conservative, 47 (62.7%) had stage 5 of kidney disease and 63 (84%) survived. From 118 children with Glomerular diseases, 68 (57.6%) were girls, 52 (44.1%) aged above 10 years, 59 (50%) had experienced 1-5 years of illness

duration, 45 (38.1%) treated HD, 86 (72.9%) had stages of stage 5 of kidney disease, and 86(72.9%) survived.

Table-3: Comparison of age, weight, height, blood measures and urine tests between survive and died children

Variables	Status	N	Mean	SD	Mean Rank	Sum of Ranks	MWU test	P value
Age	Alive	396	9.04	5.03	245.66	97281	18153	0.831
	Death	93	8.91	4.76	242.19	22524		
Weight	Alive	396	21.39	11.87	249.93	98974	16460	0.111
	Death	93	19.17	10.9	223.99	20831		
Height	Alive	396	109.77	26.63	248.77	98514.5	16919.5	0.223
	Death	93	105.98	25.77	228.93	21290.5		
Systolic Blood Pressure	Alive	393	113.02	28.72	229.25	90093.5	12672.5	<0.001
	Death	92	128.01	32.4	301.76	27761.5		
Diastolic Blood Pressure	Alive	390	72.4	16.94	229.43	89479.5	13234.5	<0.001
	Death	91	80.69	20.91	290.57	26441.5		
White blood cell (WBC)	Alive	387	8549.61	4205.56	234.01	90561.5	15483.5	0.101
	Death	90	9725.56	5082.85	260.46	23441.5		
Hemoglobin (Hb)(mg/dl)	Alive	380	9.22	2.05	246.8	93783.5	12046.5	<0.001
	Death	88	8.19	2.1	181.39	15962.5		
platelet count (mcL)	Alive	325	274156.9	137068.6	211.43	68714.5	9935.5	0.002
	Death	79	228491.1	120933.4	165.77	13095.5		
Erythrocyte Sedimentation Rate (ESR)(mm/h)	Alive	177	55.1	33.07	102.44	18131	2378	0.009
	Death	37	73.43	39.3	131.73	4874		
Blood urea nitrogen(mg/dl)	Alive	394	64.97	35.92	228.77	90136.5	12321.5	<0.001
	Death	93	84.2	36.11	308.51	28691.5		
Creatinine (mg/dl)	Alive	396	4.46	2.83	226.22	89584	10978	<0.001
	Death	93	6.67	3.33	324.96	30221		
Sodium (mEq/l)	Alive	390	138.64	5.96	245.17	95617	16898	0.306
	Death	93	137.59	6.78	228.7	21269		
Potassium (mEq/l)	Alive	392	4.67	2.87	237.51	93102.5	16074.5	0.076
	Death	93	4.73	0.96	266.16	24752.5		
Calcium (mg/dl)	Alive	384	8.75	1.2	252.53	96971.5	11508.5	<0.001
	Death	90	8.14	1.15	173.37	15603.5		
Phosphor (mg/dl)	Alive	372	5.53	1.74	230.11	85602.5	16224.5	0.65
	Death	90	5.62	1.67	237.23	21350.5		
Alkaline phosphatase (mg/dl)	Alive	312	783.79	544.21	198.35	61884.5	12839.5	0.907
	Death	83	831.88	629.7	196.69	16325.5		
pH	Alive	361	7.27	0.16	236.36	85325	12867	0.001
	Death	91	7.20	0.16	187.4	17053		
carbon dioxide	Alive	360	14.4	4.3	240.13	86447	11293	<0.001
	Death	91	11.9	4.71	170.1	15479		
parathyroid hormone (PTH) (mg/dl)	Alive	59	296.04	257.25	31.46	1856	86	0.367
	Death	4	359.25	162.75	40	160		
Glomerular filtration rate (GFR)	Alive	396	15.56	10.72	264.82	104870	10564	<0.001
	Death	93	8.87	5.65	160.59	14935		

Table-4: Main causes of hospitalization association with gender, age, duration of illness, treatment, stages of kidney disease and survival.

Variables	options	Statistic	Main Cause of CKD						Total	X2	P
			Congenital structural anomalies	cystic/hereditary/congenital disease	Glomerular diseases	Renal tubular Disease	unknown origin	stone			
Gender	Boys	n	124	39	50	18	10	13	254	13.423	0.02
		%	60.80%	52.00%	42.40%	45.00%	38.50%	50.00%	51.90%		
	Girls	n	80	36	68	22	16	13	235		
		%	39.20%	48.00%	57.60%	55.00%	61.50%	50.00%	48.10%		
Age	<1	n	21	8	6	3	0	0	38	21.304	0.127
		%	10.30%	10.70%	5.10%	7.50%	0.00%	0.00%	7.80%		
	1_5	n	36	15	16	4	3	2	76		
		%	17.60%	20.00%	13.60%	10.00%	11.50%	7.70%	15.50%		
	5_10	n	67	19	44	12	5	10	157		
		%	32.80%	25.30%	37.30%	30.00%	19.20%	38.50%	32.10%		
	>10	n	80	33	52	21	18	14	218		
		%	39.20%	44.00%	44.10%	52.50%	69.20%	53.80%	44.60%		
Duration of illness	<1y	n	30	20	26	5	6	3	90	45.769	0.106
		%	14.70%	26.70%	22.00%	12.50%	23.10%	11.50%	18.40%		
	1-5y	n	84	26	59	18	11	14	212		
		%	41.20%	34.70%	50.00%	45.00%	42.30%	53.80%	43.40%		
	>5y	n	90	29	33	17	9	9	187		
		%	44.10%	38.70%	28.00%	42.50%	34.60%	34.60%	38.20%		
Treatment	Conservative	n	105	30	29	36	9	8	217	70.769	<0.001

		%	51.50%	40.00%	24.60%	90.00%	34.60%	30.80%	44.40%		
	PD	n	42	20	32	2	7	4	107		
		%	20.60%	26.70%	27.10%	5.00%	26.90%	15.40%	21.90%		
	HD	n	45	15	45	0	9	11	125		
		%	22.10%	20.00%	38.10%	0.00%	34.60%	42.30%	25.60%		
	TX	n	12	10	12	2	1	3	40		
		%	5.90%	13.30%	10.20%	5.00%	3.80%	11.50%	8.20%		
Survival	Alive	n	169	63	86	38	20	20	396	11.59	0.041
		%	82.80%	84.00%	72.90%	95.00%	76.90%	76.90%	81.00%		
	Death	n	35	12	32	2	6	6	93		
		%	17.20%	16.00%	27.10%	5.00%	23.10%	23.10%	19.00%		
Stages of kidney disease	5	n	138	47	86	12	18	21	322	40.309	<0.001
		%	67.60%	62.70%	72.90%	30.00%	69.20%	80.80%	65.80%		
	4	n	48	19	24	16	6	3	116		
		%	23.50%	25.30%	20.30%	40.00%	23.10%	11.50%	23.70%		
	3A	n	13	7	8	11	1	1	41		
		%	6.40%	9.30%	6.80%	27.50%	3.80%	3.80%	8.40%		
	3B	n	5	2	0	1	1	1	10		
		%	2.50%	2.70%	0.00%	2.50%	3.80%	3.80%	2.00%		
	Total	n	204	75	118	40	26	26	489		
		%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%		

From 40 children with tubular renal disease, 22 (55%) were girls, 36 (90%) treated conservative, 16 (40%) had stages of kidney disease of stage 4 and 38 (95%) survived. From 26 children with unknown origin, 16 (61.5%) were girls, 18(69.2%) aged above 10 years, 11 (42%) had 1-5 years of illness duration, 9 (34.6%) treated conservative, and the same frequency was observed for those treated with HD. 18 (69.2%) had stage 5 kidney disease and 20 (76.9%) survived. From 26 children with kidney stone, 13(50%) were girls similar to boys, 14 (53.8%) aged above 10 years, 14 (53.8%) had 1- 5 years of duration in the illness, 11 (42.3%) were treated with HD, 21 (80.8%) had stage 5 kidney disease and 20 (76.9%) survived.

Table-5: Stages of kidney disease association with gender, age, duration of illness, treatment and survival

variables	options	statistics	Stages of kidney disease				Total	X2	P value
			4	5	3A	3B			
Gender	male	n	52	169	26	7	254	5.858	0.119
		%	44.80%	52.50%	63.40%	70.00%	51.90%		
	female	n	64	153	15	3	235		
		%	55.20%	47.50%	36.60%	30.00%	48.10%		
Age	<1	n	9	29	0	0	38	13.336	0.148
		%	7.80%	9.00%	0.00%	0.00%	7.80%		
	1_5	n	17	55	3	1	76		
		%	14.70%	17.10%	7.30%	10.00%	15.50%		
	5_10	n	41	102	12	2	157		
		%	35.30%	31.70%	29.30%	20.00%	32.10%		
	>10	n	49	136	26	7	218		
		%	42.20%	42.20%	63.40%	70.00%	44.60%		
Duration of illness	<1y	n	20	60	8	2	90	5.293	0.507
		%	17.20%	18.60%	19.50%	20.00%	18.40%		
	1-5y	n	47	148	15	2	212		
		%	40.50%	46.00%	36.60%	20.00%	43.40%		
	>5y	n	49	114	18	6	187		
		%	42.20%	35.40%	43.90%	60.00%	38.20%		
Treatment	Conservative	n	84	88	36	9	217	118.184	<0.001
		%	72.40%	27.30%	87.80%	90.00%	44.40%		
	Peritoneal dialysis	n	16	88	3	0	107		
		%	13.80%	27.30%	7.30%	0.00%	21.90%		
	Hemodialysis	n	12	113	0	0	125		
		%	10.30%	35.10%	0.00%	0.00%	25.60%		
	Transplant	n	4	33	2	1	40		
		%	3.40%	10.20%	4.90%	10.00%	8.20%		
Survival	Alive	n	106	240	40	10	396	26.5	<0.001
		%	91.40%	74.50%	97.60%	100.00%	81.00%		
	Death	n	10	82	1	0	93		
		%	8.60%	25.50%	2.40%	0.00%	19.00%		
	Total	n	116	322	41	10	489		
		%	100.00%	100.00%	100.00%	100.00%	100.00%		

Table 5 shows stages of kidney disease in association with gender, age, duration of illness, treatment and survival. It manifests that stages of kidney disease have significant association with treatment ($X2=118.184$, $p<0.001$) and survival ($X2=26.5$, $p<0.001$). From 322 children with stage 5 of kidney disease, 64(55.2%) were girls, 49 (42.2%) aged above 10 years, 49 (42.2%) has more than 5 years of duration in the illness, 113 (33.1%) were treated with HD and 240 (74.5%) survived. From 116 children with stage 4 of kidney disease, 169 (52.6%) were boys, 136 (42.2%) aged above 10 years, 148 (46%) had a duration of more than 5 years in the illness, 84 (72.4%) treated conservatively and 106 (91.4%) survived. From 41 children with stage 3A of kidney disease, 26 (63.4%) were boys, 26 (63.4%) aged above 10 years, 18 (43.9%) had more than 5 years duration of illness, 36 (87.8%) treated conservatively and 40 (97.6%) survived. And, out of 10 children with stage 3B of kidney disease, 7 (70%) were boys, 7 (70%) aged above 10 years, 6 (50%) had more than 5 years of illness duration, 9 (90%) treated conservatively and 10 (100%) survived.

4- DISCUSSION

The present study revealed that among clinical manifestations, edema, FTT, urinary and vomiting are more common, and congenital structural anomalies are the most common cause of hospital admission. Among the children with stage 5, the majority had conservative treatment. Those who died had higher systolic and diastolic blood pressure, higher hemoglobin (Hb), higher blood urea nitrogen, higher creatinine, lower values of platelet blood, lower urine PH, lower carbon dioxide, and risky glomerular filtration rate (GFR). In CKD children, the causes were associated with gender, treatment, stages of kidney disease and survival. Stages of kidney disease had significant associations with treatment and survival. The majority of children had conservative treatment. The hospitalization causes had significant association with gender, treatment, stages of kidney disease and survival. Stages of kidney disease had significant associations with treatment and survival.

Previous studies have reported the annual incidence of CKD as 5.52 in a million general population when this rate was 16.8 in pediatrics with variety from society to society (8) with the level of 15.5% in Cameroon (17), 14.9% in Iran (18), 20.3% in Nigeria (19) and 4% in Soudan (20) and in addition, was it found to be 0.88% and 1.2% in children with renal diseases (21, 22). Late diagnosis and late treatment in CKD children is common such that among our children with CKD, the majority aged higher than 10 years. It the mean age and the median at the time of CKD diagnosis has been reported to be 11.01and 12.5 years, respectively in one study (8) and 4.2 years in another research (23). The present study found the mean age of 9.01 years that is higher than those reported by Ahmadzadeh et al., (23) and lower than those by Gheissari et al. (8). In studies by Halle et al. (17) and Olowu et al. (24), the prevalence of CKD was higher in boys. Moreover, in the study by Soheilipour et al., (16) on CKD children that aged from 2 to16 years, the mean age was 7.97 and most of them were boys. In our study, the most common causes of CKD were congenital anomalies, glomerulopathy and hereditary tubulopathy that is in line with Soheilipour et al., (16) finding that glomerulopathy and hereditary tubulopathy were the main causes. In another study, non-glomerular kidney disease was found to be the leading cause of CKD (25). A review of the studies on children with renal failure was conducted By Halle et al. (17), in Cameroon. They concluded that persistent glomerulonephritis and urological mutations were the major causes of CKD.

In developing countries, chronic glomerulonephritis was the underlying cause of CKD, with prevalence rates ranging from 30% to 60% (9). This may be due to the high prevalence of bacterial and parasitic diseases that normally affect the kidneys in the third world regions, as opposed to the low prevalence in developing countries (9). In contrast, in one systematic review, urological malformations were the leading cause in Western countries (26).

Kara et al., (27) conducted a study to assess kidney disease profiles in Syrian refugee children and found that kidney hospitalization in children gradually increased from 3% to 69% between 2012 and 2014. In this study, one of the main causes that the majority of patients suffered from was CAKUT. Age and race have a significant role in etiology of CKD to such an extent that in children younger than 12 years, CAKUT was the main cause, and glomerular-based illness was more probable in black teenagers (28, 29). Moreover, it has been confirmed that congenital urologic malformation is the highlighted cause of CKD with about 50.4%. The other causes of CKD are hereditary nephropathies with the rate of 17.2%, glomerulonephritis with the rate of 6.5%, multisystem disorders with the rate of 4.3%, as well as miscellaneous and unknown disorders each one with the rate of 10.8% (23).

Similar to the findings of the present study, Ataei et al. (28), in a study on CKD etiology, revealed that congenital anomalies and urinary tract infection were more frequent in CKD patients, followed by cystic/ hereditary/ congenital diseases. In this study, children with glomerulopathy and unknown causes were 19.62% and 19.09%, respectively. Gheissari et al. (8), demonstrated that the main etiology of CKD was glomerulopathy with the rate of 34% and then reflux nephropathy. Huong et al. (29), found that the main causes of CKD were glomerulonephritis (66.4%) and congenital anomalies (13%). Another study reported that out of 84 children with CKD, 66 were with FTT, and 21 were severely ill. Side effects of CKD such as anemia, hyperlipidemia, hypocalcemia, and hyperphosphatemia were more frequently observed in children with CKD of glomerular origin. Similar to our results, FTT occurred in 13.9% of the patients (16).

It is easy to believe that CKD, which develops early in life results in a significant growth retardation and imbalanced failure to thrive. Infants with congenital CKD can have polyuria, salt-losing nephropathies and electrolyte disturbance, prematurity-related feeding intolerance, recurrent vomiting, and so on, which tend to respond to careful nutrition management (4). Chou et al. (25) reported uncontrolled blood pressure, anemia, hyperlipidemia, short stature, and FTT as clinical manifestations with the highest frequencies for hypertension, anemia, and hyperlipidemia, even in the early CKD stages. Odetunde et al. (30) conducted a study and found that 3.3% had CKD and that the majority of children with CKD were over 10 years old. Edema, oliguria and hypertension were the most frequently visited clinical factors, with the most common etiology being glomerular disease (63.6%). Gheissari et al. (8) found that about 74.8% of patients had stage 5 CKD at admission, and anemia was the most common anomaly. In the study by Ahmadzadeh et al, (13), the mean GFR at presentation was 33.5 while 22% of the patients had chronic renal failure. Chou et al, (25) found that most of the patients (39.0 %) had stage 1 CKD and only 5.5% were in stage 5. Huong et al. (39) revealed that 65% of patients were in the end-stage renal disease. The present study found that from amomg the children with CKD, 8.5% had stage 5, 23.7% had stage 4, about 8.4% had stage 3A and only 2% had stage

3B. Attai et al. (28) found that 13.22% of the patients received conservative treatment and about 47.93% and 6.61% received chronic hemodialysis and continuous portable peritoneal dialysis, respectively. Out of 18.74% of children who received a kidney transplant, 14.33% and 4.41% were successful, with abnormal renal function in the order presented. Eventually, about 13.50% of all patients died. The study found that the main treatment for children in the study was conservative therapy, followed by hemodialysis, peritoneal dialysis, and kidney transplantation. Halle et al. (17) found that nearly half of children in need of dialysis were unable to receive treatment, primarily due to financial problems associated with premature death. Renal replacement therapy was used in 72.3% of patients. Access to renal replacement therapy (RRT) is highly restricted in many developing countries, and it is well known that there is a large gap between those who need it and those who receive it (31). Odetunde et al. (30) found that 44.9% of children with CKD were in stages 4 and 5. Renal replacement therapy (RRT) was given in 25.5% of patients. 24% had hemodialysis when all were chronic or not receiving proper dialysis. And the mortality rate was 8.2%. In the study by Huong et al. (32), about 19.74% of the patients received peritoneal dialysis and hemodialysis, and 7 out of 152 received renal transplantation with a familial living donor. Mortality rate was 19% in the present study such that children with glomerular diseases and then renal stone were more at risk. In this regard, Halle et al. (17) found that half of the patients died in the hospital and more than 25% of the patients became untraceable. Huong et al. (29) revealed that during the hospitalization of 152 children, 5 died and 76 patients (50%) refused treatment despite being covered by health insurance. This high mortality rate can be explained by many factors, including the severity of kidney infections at the emergency department show, the effects of the underlying disorder, the lack of satisfactory settings, and the financial constraints of exactly the end-stage patients. Kidney disease in the stage of undergoing hemodialysis is necessary. It is well known that the cost of hemodialysis is exorbitant for most families (32).

The high mortality rate observed in the present study was due to causes and stages of CKD; and did not change with the levels of electrolytes. In our recent studies, we had observed that survival of ill children with AKI (patients with abnormal Na had 3.1 times higher probabilities for death) (33) and those who admitted to the PICU (34) with electrolyte abnormalities had also high probabilities for death. This may be due to body adaptation of the present study patients with electrolytes changes. The main causes and reasons for the above mentioned discussion for the differences in the etiology of CKD in different societies are the absence of early diagnosis, deficient administration in treatment and lack of proper registry system, especially in the context of the study. This research had several limitations such as losing some of the patients in the follow up or withdrawing the treatment.

5- CONCLUSION

Overall, it is concluded that among the clinical manifestations, edema, FTT, urinary and vomiting were more common and congenital structural anomalies were the most common cause of hospital admission. In our CKD children, the causes were associated with gender, treatment, stages of kidney disease and survival. Stages of kidney disease were significantly associated with treatment and survival. The hospitalization causes had significant associations with gender, treatment, stages of kidney disease and survival. Stages of kidney disease had significant associations with treatment and survival. Therefore, more attention to

children with these signs is essential for early diagnosis and proper treatment.

6- ACKNOWLEDGEMENTS

The authors would like to thank all participants and their parents for the warm and sincere corporation.

7- CONFLICT OF INTERESTS

None.

8- ETHICAL CONSIDERATIONS

After obtaining the approval from ethical committee of the university (IR.ZAUMS.REC.1399.286) children who met the inclusion and exclusion criteria enrolled in the study. A written informed consent was taken from the parents or guardians of the participating children.

9- REFERENCES

1. Brück K, Stel VS, Fraser S, De Goeij MC, Caskey F, Abu-Hanna A, Jager KJ. Translational research in nephrology: chronic kidney disease prevention and public health. Clinical kidney journal. 2015 Dec 1; 8(6):647-55.

2. Becherucci F, Roperto RM, Materassi M, Romagnani P. Chronic kidney disease in children. Clinical kidney journal. 2016 Aug 1; 9(4):583-91.

3. Cattran DC, Feehally J, Cook HT, Liu ZH, Fervenza FC, Mezzano SA, Floege J, Nachman PH, Gipson DS, Praga M, Glassock RJ, Radhakrishnan J, Hodson EM, Rovin BH, Jha V, Troyanov S, Li PKT, Wetzels JFM. Kidney disease: improving global outcomes (KDIGO) glomerulonephritis work group. KDIGO clinical practice guideline for glomerulonephritis. Kidney International Supplements. 2012 Jun 1; 2(2):139-274.

4. Warady BA, Chadha V. Chronic kidney disease in children: the global perspective. Pediatr Nephrol 2007; 22: 1999–2009.

5. Saran R, Robinson B, Abbott KC, Agodoa LY, Albertus P, Ayanian J, et al., US renal data system 2016 annual data report: epidemiology of kidney disease in the United States. American journal of kidney diseases. 2017 Mar 1;69(3):A7-8.

6. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. American journal of kidney diseases. 2003 Jan 1; 41(1):1-2.

7. Aghighi M, Mahdavi -Mazdeh M, Zamyadi M, Heidary Rouchi A, Rajolani H, Nourozi S. Changing epidemiology of end -stage renal disease in last 10 years in Iran. Iran J Kidney Dis. 2009; 3(4):192 -6.

8. Gheissari A, Kelishadi R, Roomizadeh P, Abedini A, Haghjooy-Javanmard S, Abtahi SH, Mehdikhani B, Shafiei M. Chronic kidney disease stages 3-5 in Iranian children: Need for a school-based screening strategy: The CASPIAN-III study. International journal of preventive medicine. 2013 Jan; 4(1):95.

9. Harambat J, Van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatric nephrology. 2012 Mar; 27(3):363-73.

10. Vivante A, Hildebrandt F. Exploring the genetic basis of early-onset chronic kidney disease. Nat Rev Nephrol 2016; 12: 133–146.

11. Ding W, Cheung WW, Mak RH. Impact of obesity on kidney function and blood pressure in children. World J Nephrol 2015; 4: 223–229.

12. Hooman N, Esfahani ST, Mohkam M, Derakhshan A, Gheissari A, Vazirian S,Mortazavi Ghane-Sherbaff F, Falak-Aflaki B, Otoukesh H, Madani A, Sharifian-Dorcheh M, Mahdavi A, Esmaeile M, Naseri M, Azhir A, Merikhi A, Mohseni P, Ataei N, Fallahzadeh MH, Basiratnia M, Hosseini-Al-Hashemi G, The outcome of Iranian children on continuous ambulatory peritoneal dialysis: the first report of Iranian National

Registry. Arch Iran Med. 2009; 12(1):24 - 8. 9.

13. Ahmadzadeh A, Valavi E, Kamali M, Ahmadzadeh Azin. Chronic Kidney Disease in Southwestern Iranian Children. Iranian Journal of Pediatrics 2009. 19(2):147 -153.

14. Rodig NM, McDermott KC, Schneider MF, Hotchkiss HM, Yadin O, Seikaly MG, Furth SL, Warady BA. Growth in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children Study. Pediatric Nephrology. 2014 Oct; 29(10):1987-95.

15. Gat-Yablonski G, Phillip M. Nutritionally-induced catch-up growth. Nutrients 2015; 7: 517–551.

16. Soheilipour F, Hooman N, Ahmadvand P. Prevalence of Failure to Thrive in Iranian Children with Chronic Kidney Disease. Journal of Pediatric Nephrology. 2017; 5(3).

17. Halle MP, Lapsap CT, Barla E, Fouda H, Djantio H, Moudze BK, Akazong CA, Priso EB. Epidemiology and outcomes of children with renal failure in the pediatric ward of a tertiary hospital in Cameroon. BMC pediatrics. 2017 Dec 1; 17(1):202.

18. Derakhshan A, Al Hashemi GH, Fallahzadeh MH. Spectrum of in-patient renal diseases in children "a report from southern part Islamic Republic of Iran". Saudi Journal of Kidney Diseases and Transplantation. 2004; 15(1):12.

19. Ocheke IE, Okolo SN, Bode-Thomas F, Agaba EI. Pattern of childhood renal diseases in Jos, Nigeria: a preliminary report. Journal of Medicine in the Tropics. 2010; 12(2).

20. Ali E-TM, Rahman AH, Karrar ZA. Pattern and outcome of renal diseases in hospitalized children in Khartoum state. Sudan Sudanese Journal of Paediatrics. 2012; 12(2):52.

21. Elzouki AY, Amin F, Jaiswal OP. Prevalence and pattern of renal disease in eastern Libya. Arch Dis Child 1983; 58:106-9.

22. Yadav SP, Shah GS, Mishra OP, Baral N. Pattern of renal diseases in children: A developing country experience. Saudi Journal of Kidney Diseases and Transplantation. 2016 Mar 1; 27(2):371.

23. Ahmadzadeh A, Valavi E, ZANGENEH KM, Ahmadzadeh A. Chronic kidney disease in Southwestern Iran J Pediatr. 2009; 19 (2); 147-153.

24. Olowu WA, Niang A, Osafo C, Ashuntantang G, Arogundade FA, Porter J, Naicker S, Luyckx VA. Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic review. Lancet Glob Health. 2016; 4(4):e242–e50.

25. Chou HH, Lin CY, Chiou YH, Tain YL, Wang YF, Wang HH, Chiou YY. Clinical characteristics and prevalence of complications of chronic kidney disease in children: The Taiwan Pediatric Renal Collaborative study. Pediatric Nephrology. 2016 Jul 1; 31(7):1113-2.

26. Van der Heijden BJ, van Dijk PC, Verrier-Jones K, Jager KJ, Briggs JD. Renal replacement therapy in children: data from 12 registries in Europe. Pediatr Nephrol. 2004; 19(2):213–21.

27. Kara MA, Kilic BD, Çöl N, Özçelik AA, Büyükçelik M, Balat A. Kidney disease profile of Syrian refugee children. Iranian Journal of Kidney Diseases. 2017 Mar 1; 11(2):109.

28. Ataei N, Hosseini M, Baikpour M, Ataei F, Bloori Jirandeh H, Bazargani B, Yousefifard M, Abbasi A. Etiology and outcome of chronic kidney disease in iranian children. International Journal of Pediatrics. 2016; 4(7):2105-12.

29. Huong NTQ, Long TD, Bouissou F, Liem NT, Truong DM, Nga DK, Chien TT, Bascands JL, Chronic kidney disease

in children: the National Paediatric Hospital experience in Hanoi, Vietnam. Nephrology. 2009 Dec; 14(8):722-7.

30. Odetunde OI, Okafor HU, Uwaezuoke SN, Ezeonwu BU, Adiele KD, Ukoha OM. Chronic kidney disease in children as seen in a tertiary hospital in Enugu, South-East, Nigeria. Nigerian journal of clinical practice. 2014 Mar 27; 17(2):196-200.

31. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, Zhao MH, Lv J, Garg AX, Knight J, Rodgers A, Gallagher M, Kotwal S, Cass A, Perkovic V. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet. 2015; 385(9981):1975–82.

32. Obiagwu PN, Abdu A. Peritoneal dialysis vs. haemodialysis in the management of paediatric acute kidney injury in Kano, Nigeria: a cost analysis. Tropical Med Int Health. 2015; 20(1):2–7.

33. Sadeghi-Bojd S, Noori NM, Mohammadi M, Teimouri A. Clinical characteristics and mortality risk prediction in children with acute kidney injury. Nigerian medical journal: journal of the Nigeria Medical Association. 2015; 56(5):327.

34. Sadeghi-Bojd S, Noori NM, Damani E, Teimouri A. Electrolyte disturbances in PICU: A cross sectional study. Nephro-Urology Monthly. 2019; 11(2).