Original Article

Outcome of Patients having Congenital Anomalies of the Kidney and Urinary Tract Associated with Congenital Heart Diseases in Pediatric Cardiac ICU.

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Abstract

Introduction: Congenital heart defects are the most common of all congenital malformations and there is a higher incidence of urinary tract anomalies in these cases
Aim of the study: Our study aims to identify the prevalence and phenotypes of congenital anomalies of the kidney and urinary tract (CAKUT) among cases with congenital heart diseases admitted to cardiac ICU.
Methods: Eighty seven neonates and infants with congenital heart diseases were admitted to the cardiac ICU. Patients were assessed for CAKUT mainly via pelvi-abdominal US screening to exclude gross anomalies, along with clinical, laboratory and other imaging findings during the PICU admission.
Results: Patients diagnosed with CAKUT formed 9.2%. Although there was no statistical correlation between certain types of congenital heart diseases (CHD) and certain types of CAKUT, there was a higher incidence among patients with cyanotic CHD (11.3%) rather than in patients with acyanotic heart CHD (6.9%). There was a strong correlation between the presence of CAKUT and the length of PICU stay, the need for higher doses of inotropes and the need for renal dialysis. There was a higher incidence with positive history of maternal chronic illness and maternal drug intake during pregnancy.
Conclusion: CAKUT is common among patients admitted into the PICU with CHD. CAKUT is associated with increased morbidity, length of PICU stay and poor outcome. Pelvi-abdominal US is one of the gold standard tools for screening.

Key words: Congenital Anomalies of Kidney and Urinary Tract, Congenital Heart Disease, Pelvi-Abdominal Ultrasonography, PICU.
Running title: Association between Congenital Anomalies of the Kidney and Urinary Tract and Congenital Heart Disease.

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Introduction

Congenital heart defects are the most common of all congenital malformations, with a reported incidence of 6 to 8 per 1000 live births. The Centers for Disease Control reports cyanotic heart defects occurred in 56.9 per 100,000 live births in the United States in 2005 [1].

Most congenital heart defects are well tolerated in the fetus because of the parallel nature of the fetal circulation. It is only after birth when the fetal pathways (ductus arteriosus and foramen ovale) begin to close that the full hemodynamic impact of an anatomic abnormality becomes apparent [2].

The cause of most congenital heart defects is unknown. Most cases of congenital heart disease were thought to be multifactorial resulting from a combination of genetic predisposition and environmental stimulus. A small percentage of congenital heart lesions are related to chromosomal abnormalities, in particular, trisomy 21, 13, and 18 and Turner syndrome. Heart disease is found in more than 90% of patients with trisomy 18, 50% of patients with trisomy 21, and 40% of those with Turner syndrome [2].

On the other hand, Congenital anomalies of the kidney and urinary tract anatomy are common in children and represent approximately 30% of all prenatally diagnosed malformations. They are phenotypically variable and can affect the kidney(s) alone and/or the lower urinary tract. The spectrum includes more common anomalies such as vesicoureteral reflux and, rarely, more severe malformations such as bilateral renal agenesis [3].

Renal agenesis, or absent kidney development, can occur secondary to a defect of the wolffian duct, ureteric bud, or metanephric blastema. Bilateral renal agenesis is incompatible with extrauterine life and produces the Potter syndrome. Approximately 15% of these children have contralateral vesicoureteral reflux [4].

Renal dysgenesis refers to maldevelopment of the kidney that affects its size, shape, or structure. Renal hypoplasia refers to a small non-dysplastic kidney with fewer than the normal number of calyces and nephrons [5]. If cysts are present, the condition is termed cystic dysplasia. If the entire kidney is dysplastic with a preponderance of cysts, the kidney is referred to as a multicystic dysplastic kidney (MCDK) [6, 7]. Ectopic kidney may be in a pelvic, iliac, thoracic, or contralateral position. The incidenc.e of renal ectopia is approximately 1 in 900 [5]. Renal fusion anomalies (horseshoe kidney) occur in 1/400-500 births and in 7% of patients with Turner syndrome [8].

Although congenital anomalies of the kidney and urinary tract (CAKUT) are known to occur in children with cardiovascular malformations (CVM) in syndromic or non-syndromic patterns, there are only a few studies, which have described the frequency of occurrence of CAKUT associated with CMV and the exact relationship between the malformations of these two systems [9].

Aim of the Work was to study the prevalence and phenotypes of congenital anomalies of the kidney and urinary tract (CAKUT) among neonates, infants & children with congenital heart diseases admitted to cardiac intensive care unit.

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Methods

In this study we prospectively enrolled 87 patients (neonates & infants) who were admitted with congenital heart diseases, over the period of 12 months from April 2018 to April 2019 in the Cardiac intensive care unit in Specialized Children's Hospital, Egypt. Informed consent was obtained from parents/guardians of neonates and infants enrolled in the study. **Inclusion Criteria** All patients diagnosed with congenital heart diseases admitted to the cardiac intensive care unit in Aboul Rish Children's Hospital, from day 1 of life to 12 years old, over 12 months from April 2018 to April 2019 with a sample size of 87 patients.

Data Collected from Patients Included

1. History taking, with emphasis on:
   a- Family history: of congenital anomalies.
   b- Prenatal history: Maternal age at conception, chronic illness in mother, drug intake during pregnancy & history of fever, rash, positive TORCH.
   c- Natal history: gestational birth, the duration of labor, anomalies of the amniotic fluid or with single umbilical artery.
   d- Postnatal history: APGAR score or resuscitation history of the newborn.
2. Vital data & PICU stay:
   a- Herat rate, Arterial blood pressure, Respiratory rate, Body temperature.
   b- Need for mechanical ventilation.
   c- Need for renal dialysis.
   d- Need for inotropes. Need for higher dose of inotropes (Dopamine >10 mic/kg/min, Doputamine >10 mic/kg/min, Noradrenaline >0.1 e- mic/kg/min and Adrenaline infusion at any dose).
   f- Number of days needed in PICU. Need for long PICU admission considered if > 7 days
3. Laboratory investigations, including CBC, CRP, Kidney functions, serum electrolytes.
4. Imaging studies, including
   a- Echocardiography covering: Conclusion of anatomical diagnosis, ejection fraction (EF %) and fraction of shortening (FS %).
   b- Abdominal & pelvic ultrasonography including: Length of both kidneys, Site of both kidneys, Renal Echogenicity, Presence of back-pressure signs, Presence of renal stones and Presence of renal cysts.
   c- Plain X-ray of chest & abdomen.
   d- Electrocardiography

Statistical analysis

All the collected data were revised for completeness and logical consistency. Pre-coded data was entered on the computer using Microsoft Office Excel Software Program 2016. Pre-coded data was then transferred and entered into IBM© SPSS© (Statistical Package of Social Science Software program) version 25 (IBM© Corp., Armonk, NY, USA) to be statistically analyzed. For qualitative variables, they were described as frequency and percentage. Comparison forqualitative variables were by using chi square test and fisher exact test, where p-value of significant correlation if $p < 0.05$. For quantitative variables, they were described as mean ± SD and median, IQR (interquartile range) (25th and 75th percentiles). Comparison for quantitative variables were by using independent t test,

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where p-value of significant correlation if $p < 0.05$.

Results

This study conducted on 87 patients admitted from Cardiac Pediatric Intensive Care Unit, Abo El Reesh Hospital, Cairo University, in the period from April 2018 to April 2019.

They were 37 females (42.5%) and 50 males (57.5%) with age ranged from 0.12 - 30 months with median of 3 months. In this study weight of the patients ranged from 2 - 15 kg with mean weight of 4.2 kg. The height of the patients ranged from 48 cm to 86 cm with mean height of 57.8 cm.

In our study, we had 44 patients (50.6%) with congenital cyanotic heart disease and 43 patients (49.4%) with congenital acyanotic heart disease. While regarding renal condition, we had 79 patients (90.8%) with normal renal phenotype and 8 patients (9.2%) with abnormal renal phenotype.

Regarding renal ultrasound findings **(Table 1)**, **(Figure 1)** Right renal length ranged from 3.71 cm to 8.8 cm, with a mean of 5.39 cm (z-score ranged from -9.18 to 5.03), while left renal length ranged from 3.9 cm to 9.3 cm, with a mean of 5.53 cm as well (z-score ranged from -2.61 to 5.18).

Normal site of the kidneys was found in 96.6% of patients (84 patients), while renal ectopia was found in 2.2% of patients (2 patients), and renal agenesis was found in 1.1% of patients (1 patient) **(Figure 2)**.

In patients with renal back pressure, Right and left renal parenchymal thickness was measured **(Table 1)**. None of the patients showed renal stones, cysts, nor urinary bladder anomalies.

Table 1: Abdominal-pelvic U/S findings of the studied cases

Abdomino -pelvic U/S		Total No. = 87
Rt kidney length (cm)	Mean ± SD	5.39 ± 1.11
	Range	3.71 – 8.8
Rt kidney length (z-score)	Median (IQR)	-0.22 (-1.16 – 0.34)
	Range	-9.18 – 5.03
Lt Kidney length (cm)	Mean ± SD	5.53 ± 0.91
	Range	3.9 – 9.3
Lt Kidney length (z-score)	Median (IQR)	-0.05 (-1.03 – 0.33)
	Range	-2.61 – 5.18
Site	Normal	84 (96.6%)
	Rt pelvic	1 (1.1%)
	Rt renal agenesis	1 (1.1%)
	Lt pelvic	1 (1.1%)
Echogenecity	Normal	83 (95.4%)
	Nephropathy grade I	3 (3.4%)
	Nephropathy grade II	1 (1.1%)
Back pressure	Negative	82 (94.3%)
	Positive	5 (5.7%)
Rt Parynchymal thickness (cm)	Mean ± SD	1.36 ± 0.27
	Range	1 – 1.7
Lt Parynchymal thickness (cm)	Mean ± SD	1.13 ± 0.14
	Range	1 – 1.3
Rt Pelvic A/P diameter (cm)	Mean ± SD	0.91 ± 0.27
	Range	0.6 – 1.3
Lt Pelvic A/P diameter (cm)	Mean ± SD	1.03 ± 0.32
	Range	0.6 – 1.5
Stones	Negative	87 (100.0%)
Cysts	Negative	87 (100.0%)
Urinary Bladder anomalies	Negative	87 (100.0%)

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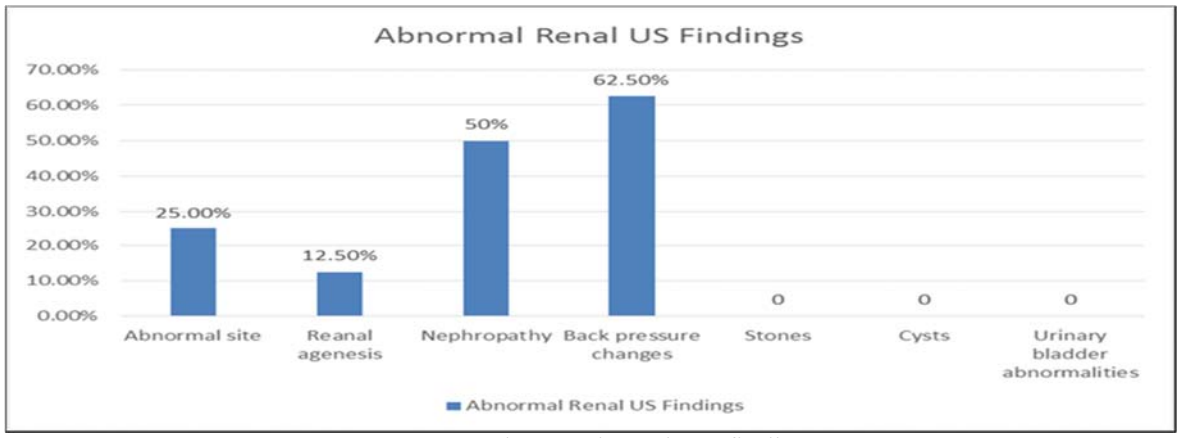

Figure 1: Abnormal renal US findings.

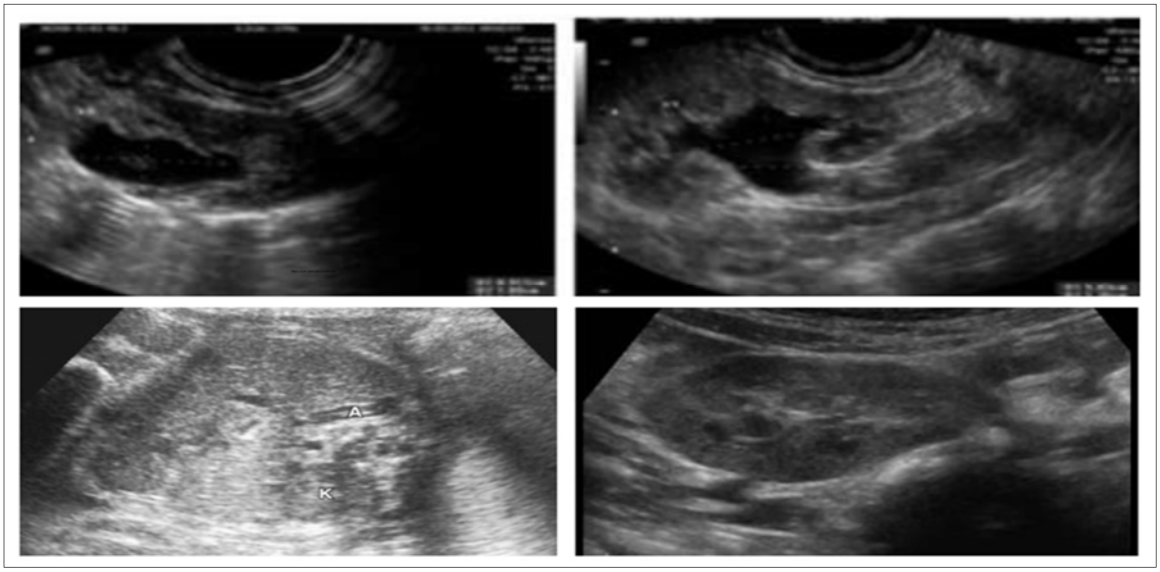

Figure 2: Renal U/S views of some of studied cases, A. long-axis view of hydronephrosis (marked dilation of the calices and renal pelvis), B. transverse (short axis) view of hydronephrosis, C. transverse view of unilateral renal agenesis showing fetal adrenal gland, D. left pelvic kidney.

Relation between Renal Condition and Demographic Data

As shown in Table 2 that there was no statistically significant relationship found between renal phenotype of the studied cases and their demographic data.

Relation between Renal Condition and Congenital Heart

In our study, all studied patients had some form of congenital heart disease, of which only 9.2% had CAKUT. Of the studied patients, 79 patients had a normal renal phenotype, of which, 40 patients (50.6%) had acyanotic congenital heart disease, and 39 patients (49.4%) had cyanotic congenital heart disease **(Table 3)**. Patients with an abnormal renal phenotype were 8 patients, of which 3 patients (37.5%) had acyanotic congenital heart disease, and 5 patients (62.5%) had cyanotic congenital heart disease **(Figure 3)**. There was no statistically significant difference between renal condition and congenital heart with p-value of 0.48.

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Table 2: Relation between renal phenotype and demographic data of the studied cases

Variable		Renal Phenotype		Test value	P-value	Sig.
		Normal	Abnormal			
		No. = 79	No. = 8			
Sex	Females	34 (43.0%)	3 (37.5%)	0.091*	0.763	NS
	Males	45 (57.0%)	5 (62.5%)			
Age (months)	Median (IQR)	3 (1.2 – 5.04)	3.96 (2.04 – 4.5)	−0.192≠	0.848	NS
	Range	0.12 – 30	0.24 – 5.04			
Height / Length (cm)	Mean ± SD	58.95 ± 12.95	59.13 ± 4.85	-0.038•	0.970	NS
	Range	48 – 140	50 – 63			
Weight (kg)	Median (IQR)	3.5 (3 – 4.7)	3.2 (2.9 – 4.5)	−0.803≠	0.422	NS
	Range	2 – 40	2.6 – 5.5			

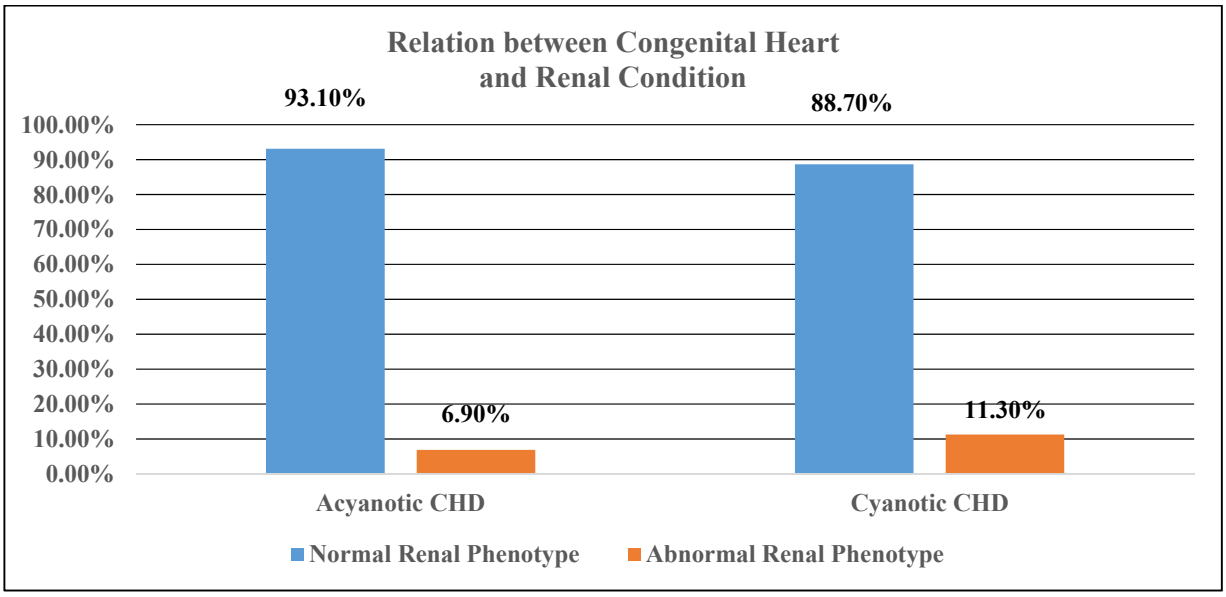

Figure 3: Relation between congenital heart and renal condition.

Table 3: Diagnoses of CHD in patients found with CAKUT

No	Age in months	Sex	Weight in kg	Type of CHD	Diagnosis of CHD	Renal Phenotype
1	5	male	4	cyanotic	singe ventricle, mitral atresia, malposed great vessels	Rt ectopic kidney
2	0.27	male	3	cyanotic	DORV, malposed geat vessels, interrupted aortic arch	bilateral hydronephrosis
3	1.13	female	2.8	cyanotic	D-TGA	bilateral hydronephrosis
4	4	male	3.4	cyanotic	DORV, CAVC, PDA, PS	bilateral hydronephrosis
5	4	male	5	acyanotic	ASD, VSD	bilateral hydronephrosis
6	3	female	3	acyanotic	VSD	Lt hydronephrosis
7	5	female	5.5	cyanotic	DILV, malposed great vessels	Rt renal agenesis
8	4	male	2.6	cyanotic	D-TGA	Lt ectopic kidney

Relation between renal condition and maternal history

In the studied cases, the mean maternal age within the cases with normal

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phenotype was 28.47 years with a standard deviation of 4.6 years, while the mean maternal age within the cases with CAKUT was 32.88 years with a standard deviation of 6.47 years **(Table 4).**

Among cases with normal phenotype, 76 of cases (96.2%) had no history of chronic maternal illness during pregnancy and 3 cases (3.8%) had positive history of chronic maternal illness during pregnancy. While within cases with CAKUT, 5 of cases (62.5%) had no history of chronic maternal illness during pregnancy and 3 cases (37.5%) had positive history of chronic maternal illness during pregnancy. As well within cases with normal renal phenotype, 77 patients (97.5%) had no history of drug intake during pregnancy and 2 patients (2.5%) had positive history of maternal drug intake during pregnancy. While within cases with abnormal renal phenotype, 3 cases (37.5%) had no history of maternal drug intake during pregnancy and 5 cases (62.5%) had positive history of drug intake during pregnancy.

Regarding maternal history of fever, rash and positive TORCH screen, all cases were negative with no relevant relation to renal anomalies. There was a statistically significant difference between renal condition and maternal age at conception, history of chronic maternal illness during pregnancy and history of maternal drug intake during pregnancy with p-value of 0.015, <0.001 and <0.001 respectively **(Table 5)**.

Relation between renal condition and clinical data

In our study, among the studied cases with normal renal phenotype, 23 cases (29.1%) needed mechanical ventilator **(Table 6)**, while 56 cases (70.9%) had no need for mechanical ventilation, 6 cases (7.6%) needed higher doses of inotropes, while 73 cases (92.4%) did not need high doses of inotropes, 5 cases (6.3%) needed renal dialysis, while 74 cases (93.7%) had no need for renal dialysis, 12 cases (15.2%) needed longer ICU admission (> 7 days), while 67 cases (84.8%) had no need for longer ICU admission.

On the other hand, among the cases that were diagnosed with CAKUT, 4 cases (50%) needed mechanical ventilator, while 4 cases (50%) had no need for mechanical ventilation, 1 case (12.5%) needed higher doses of inotropes, while 7 cases (87.5%) did not need high doses of inotropes, 2 cases (25%) needed renal dialysis, while 6 cases (75%) had no need for renal dialysis, 5 cases (62.5%) needed longer ICU admission (> 7 days), while 3 cases (37.5%) had no need for longer ICU admission.

For the outcome (Fig. 10), by the end of the study, among the cases with normal renal phenotype, 70 patients (88.6%) were alive and 9 dead patients (11.4%), while within the patients with CAKUT, we had 4 living patients (50%) and 4 dead patients (50%).

There was a statistically significant relationship between renal condition and the need for PICU admission longer than 7 days and the outcome with p-value of 0.001 and 0.004 respectively.

Relation between Renal Condition and Laboratory Findings

In our study, there was no statistically significant relationship between renal condition and hemoglobin level, total leucocytic count, platelets count, CRP level, blood urea level, serum creatinine

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level, creatinine clearance, serum Sodium level, serum Potassium level and urinalysis with p-value of each > 0.05.

Table 4: Clinical history of the studied cases

History		Total no. = 87
Prenatal History		
Maternal age at conception (years)	**Mean ± SD** **Range**	28.87 ± 4.94 19 – 42
Maternal chronic illness	**Negative**	81 (93.1%)
	HTN	5 (5.7%)
	HTN & DM	1 (1.1%)
Drug intake	**Negative**	82 (94.3%)
	Alpha methyl-dopa	4 (4.6%)
	Insulin	1 (1.1%)
Fever	**Negative**	87 (100.0%)
Rash	**Negative**	87 (100.0%)
Positive TORCH	**Negative**	87 (100.0%)
Natal History		
Gestational Age	**Pre term**	11 (12.6%)
	Full term	76 (87.4%)
Anomalies of amniotic fluid	**Negative**	85 (97.7%)
	Oligohydramnios	2 (2.3%)

Table 5: Relation between renal condition and maternal history

History		Renal Phenotype		Test value	P-value	Sig.
		Normal	**Abnormal**			
		No. = 79	**No. = 8**			
Prenatal History						
Maternal age at conception (years)	**Mean ± SD**	28.47 ± 4.62	32.88 ± 6.47	-2.477•	0.015	S
	Range	19 – 41	23 – 42			
Family	**Negative**	79 (100.0%)	8 (100.0%)	–	–	–
Maternal chronic illness	**Negative**	76 (96.2%)	5 (62.5%)	16.444 *	0.000	HS
	HTN	3 (3.8%)	2 (25.0%)			
	HTN & DM	0 (0.0%)	1 (12.5%)			
Drug intake	**Negative**	77 (97.5%)	5 (62.5%)	18.794 *	0.000	HS
	Alpha methyl-dopa	2 (2.5%)	2 (25.0%)			
	Insulin	0 (0.0%)	1 (12.5%)			
Fever	**Negative**	79 (100.0%)	8 (100.0%)	–	–	–
Rash	**Negative**	79 (100.0%)	8 (100.0%)	–	–	–
Positive TORCH	**Negative**	79 (100.0%)	8 (100.0%)	–	–	–
Natal History						
Gestational Age	**Pre term**	9 (11.4%)	2 (25.0%)	1.218*	0.270	NS
	Full term	70 (88.6%)	6 (75.0%)			
Anomalies of amniotic fluid	**Negative**	77 (97.5%)	8 (100.0%)	0.207*	0.649	NS
	Oligohydramnios	2 (2.5%)	0 (0.0%)			

Table 6: Relation between renal condition and clinical data.

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PICU Stay		Renal Phenotype		Test value	P-value	Sig.
		Normal	Abnormal			
		No. = 79	No. = 8			
Need for MV	No	56 (70.9%)	4 (50.0%)	1.481*	0.224	NS
	Yes	23 (29.1%)	4 (50.0%)			
Need for high doses of inotropes	No	73 (92.4%)	7 (87.5%)	0.236*	0.627	NS
	Yes	6 (7.6%)	1 (12.5%)			
Need for dialysis	No	74 (93.7%)	6 (75.0%)	3.423*	0.064	NS
	Yes	5 (6.3%)	2 (25.0%)			
Need for longer admission (<7 days)	No	67 (84.8%)	3 (37.5%)	10.342*	0.001	HS
	Yes	12 (15.2%)	5 (62.5%)			
Outcome	Alive	70 (88.6%)	4 (50.0%)	8.519*	0.004	HS
	Died	9 (11.4%)	4 (50.0%)			

Discussion

Although congenital anomalies of the kidney and urinary tract (CAKUT) are known to occur in children with cardiovascular malformations (CVM) in syndromic or non-syndromic patterns, there are only a few studies, which have described the frequency of occurrence of CAKUT associated with CMV and the exact relationship between the malformations of these two systems [9].

We have studied a cohort of 87 children with congenital heart disease who were screened for CAKUT. In our study, we addressed the incidence of CAKUT, maternal history factors, clinical data & PICU admission criteria that were associated with CAKUT in these patients.

The incidence of CAKUT in our cohort study was 9.2%, literatures showed a range for the incidence of CAKUT in children with CHD ranging between 7.4% to 11.9% [10] and (Murugasu al., 1990) [11] .

Other studies showed a higher incidence of CAKUT in children with CHD than our study especially when the cases were restricted to those with extracardiac malformations submitted to autopsy (23.1%) and (35.8%) [12].

In 2015, Stoll and others studied reported that Anomalies in the urinary tract were the most common other anomalies. CAKUT constituted for 238 of 1197 (20%) non cardiac major anomalies [13]. As well, Amorim and others published a study in 2008, 277 newborns and 75 stillbirths with CHD diagnosed from 1990 to 2003 Brazil, were evaluated. The CHD was confirmed by postnatal echocardiography or necropsy. The most common extracardiac were those of the genitourinary system (48.3%) [14].

In our study, the cardiac diagnoses of the patients were 44 child (50.6%) with congenital cyanotic heart disease and 43 child (49.4%) with congenital acyanotic heart disease. The Echo findings of these congenital cardiac conditions showed that the incidence of PDA was the highest in 40.2% of patients, followed by VSD in 35.6% of patients, ASD in 34.5% of patients, TGA was found in 19.2% of patients, common AV canal in 12.6% of patients, DORV was found in 11.5% of patients and TOF in 6.9% of patients.

In 2015, Stoll and others studied CHD in all live births, stillbirths and terminations of pregnancy during 26 years in 346,831 consecutive pregnancies. Of the cases born during this period, 4005 cases were diagnosed with CHD (total prevalence of 115.5 per 10,000) and 1055 (26.3%) had associated other major anomalies. In the identified CHD, the

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most frequent CHD were VSD (38%), ASD (13%), PS and atresia (7%), CoA (5%), TGA (4.5%), AVSD (3%), AS and atresia (3%), and HLH (3%) [13].

While in 2002, Stephensen and others conducted a study on 740 children were diagnosed with a CHD or 1.7% of live born children. The distribution of the defects was VSD 338 (45.7%), ASD 90 (12.2%), PDA 85 (11.5%), coarctation of the aorta 28 (3.8%), TOF 22 (3.0%), transposition of the great arteries 14 (1.9%), aortic stenosis 11 (1.5%), common atrioventricular septal defect 10 (1.4%) and hypoplastic left heart syndrome 5 (0.7%) [15].

In 2005, Güçer and others retrospectively analyzed 305 autopsies of children born alive and diagnosed with congenital heart disease in a hospital in Turkey, out of 3,320 autopsies performed during the period of this study. The frequency of congenital heart disease was 9.1%. VSD was the most common cardiac malformation (15.3%), followed by ASD and TGA at rates of 10.8% and 9.8%, respectively. CoA was noted in 7.5%. Single ventricle was determined in 7% of cases and TAPVR was observed in 2.6% [16].

As well in 2010, Dilber and Malcić conducted a study in Croatia during a period of 5 years. Between October 1, 2002 and October 1, 2007, there were 205,051 live births in Croatia, 1,480 of which were patients diagnosed with congenital heart disease (0.72%). The distribution was made up of 34.6% children with VSD, 15.9% with ASD, 9.8% with PDA, 4.9% with pulmonary valvar stenosis, 3.3% with TOF, 3.3% with TGA, 3.3% with aortic stenosis, 3.2% with aortic coarctation, 4.3% with atrioventricular septal defect and common AV canal [17].

In our study, the most common CAKUT associated with cardiac malformations were backpressure changes, renal ectopy and renal agenesis (62.5%, 25% and 12.5%) respectively of patients with renal malformations. Meanwhile in 2018, Hamadah and his colleagues conducted a study in Saudi Arabia. After screening of 100 children with CHD with renal US, they identified in 94 cases (94%) normal right and left kidney in the standard sonographer shape within the renal fossae. In 6 cases investigation revealed ectopic kidney in 3 patients (50%), solitary functional kidney in 2 patients (33%) and bilateral hydronephrosis in one patient (17%) [18].

In 1987, Kramer and his colleagues prospectively evaluated 1,016 CHD up to 16 years old in Germany. A urogram following angiography was performed in 302 individuals for screening of malformations, and revealed abnormalities of the upper urinary tract in 8.9%. The most frequent anomalies of the urinary tract reported were the total kidney duplication and the duplication of the ureter or renal pelvis [19].

In 2009, Gonzalez and his colleagues conducted a retrospective analysis of the medical charts of 223 neonates with a prenatal diagnosis of structural CHD from 1998 to 2007. The CHD was confirmed by postnatal echocardiography. Abdominal ultrasound (performed in 58.7% of the cases) detected some abnormality in 41.2% of the cases, 36.6% were clinically significant, most of them consisting of renal malformations [20].

In 1989, Stoll and his colleagues studied 801 newborns with CHD and a

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control group in France. The study included fetuses and stillbirths. The most frequent extracardiac malformation affected the urinary tract (21.4%). The most frequent abnormalities of the upper renal system were the urethral anomalies, hydronephrosis and unilateral renal [21].

As mentioned before, Murugasu and others conducted a prospective study in Singapore in 1990, including 109 children with CHD. CAKUT were found in 11.9% of the children. Renal anomalies included hydronephrosis, duplication, ectopy, agenesis and renal dysplasia. None of the children had any signs or symptoms suggestive of urinary tract disease. It was concluded that early identification of the urologic anomalies in these patients would only have been possible using a screening test [11].

Although there was no clear association in our study between certain types of CHD and certain types of CAKUT, there was a higher incidence of CAKUT associated with cyanotic CHD, rather than the incidence of CAKUT associated with acyanotic CHD (11.3% and 6.9%) respectively.

In the mentioned before retrospective study by Miller and other in 2011, 7,984 patients were evaluated. The urinary systems birth defects counted for (23.1%). The authors observed a higher frequency of specific combinations, such as hydronephrosis or urethral atresia with cardiac malrotation, right ventricular outlet obstruction and interventricular communication [12].

In 2003, Calzolari and others carried out a retrospective study of 1,549 live births or deaths with congenital heart disease in Italy. Extra cardiac malformations were found in 26% of cardiac patients. Interventricular and interatrial ostium secundum communication and complex heart disease were the cardiac lesions most often associated with extra cardiac malformations, of which genitourinary malformations counted for 22.9% [22].

Also in 2005, Wojtalik and others studied 1,856 children admitted for cardiac surgery in a pediatric tertiary center in Poland, from 1997 to 2002. Extra cardiac lesions were found in 84 children (4.5%), of which 22.4% had some sort of CAKUT, as it was the most frequent extra cardiac malformation. As well, more non-cardiac malformations were observed in children with a ventricular septal defect (7.6%) [23].

In the mentioned before study, in 2005, Güçer and others retrospectively analyzed 305 autopsies of children born alive and diagnosed with congenital heart disease in Turkey. In 45.9% of cases, one or more extra cardiac malformations were present. Genitourinary malformations were present in 15.1% of them. Interatrial and interventricular communications, coarctation of the aorta, single ventricle, pulmonary stenosis, hypoplastic right heart syndrome and DORV were frequently accompanied by extra cardiac malformations (>50%). In addition, abnormalities of the genitourinary systems were often found in association with conotruncal defects [17].

In our studied cohort of patients, admitted in PICU with CHD, there was need for renal dialysis in eight patients (8%). Among the cases with normal renal phenotype, 5 of 79 patients needed renal dialysis (6.3%), while 2 of 8 patients needed renal dialysis (25%) among the cases that were diagnosed with CAKUT.

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In 2007, Morelli and others studied the neonates with congenital heart disease admitted to their ICU over a period of 6 months for the need of renal dialysis. The incidence of acute renal failure and the need for renal dialysis were equivalent and occurred in 10% of admitted cases [24].

Our study results showed that among cases with normal phenotype, 76 of cases (96.2%) had no history of chronic maternal illness during pregnancy (gestational and pregestational diabetes mellitus and gestational hypertension) and 3 cases (3.8%) had positive history of chronic maternal illness during pregnancy. While within cases with CAKUT, 5 of cases (62.5%) had no history of chronic maternal illness during pregnancy and 3 cases (32.5%) had positive history of chronic maternal illness during pregnancy.

In 2015, Dart and others studied 945 case patients with CAKUT and 4,725 controls were identified. Maternal pregestational DM was found in 4.1% of the CAKUT group and 2.3% controls, whereas gestational DM occurred in 4.2% of the CAKUT group and 3.3% controls [25]. As well in 2011, Shnorhavorian and his colleagues studied 4673 cases with CAKUT and 18,692 controls for maternal factors are associated with the risk of CAKUT. Studied risk factors were all associated with an increased risk of kidney anomalies. In the CAKUT group, gestational diabetes in 4.1%, preexisting diabetes in 1.0% and maternal renal disease in 0.6% of cases. In the control group, gestational diabetes in 3.4%, preexisting diabetes in 0.5%, and maternal renal disease in 0.1% of cases. These risk factors were associated with the risk of ureter, bladder, and urethra anomalies [26].

In our study, within cases with normal renal phenotype, 77 patients (97.5%) had no history of drug intake during pregnancy and 2 patients (2.5%) had positive history of maternal drug intake during pregnancy. While within cases with abnormal renal phenotype, 5 cases (62.5%) had no history of maternal drug intake during pregnancy and 3 cases (32.5%) had positive history of drug intake during pregnancy.

In 2003, Abe and others evaluated 192 infants with renal anomalies and 3029 infant without birth defects, all of whom were born from 1968 through 1980, for the effect of maternal febrile illnesses and medication use on renal anomalies. The incidence of antipyretic medications use during pregnancy was found to be higher in the CAKUT group (5.7%) than in the control group (2.7%), while the incidence of antibiotics use during pregnancy was found to be higher as well in CAKUT group (5.2%) than in the control group (2.5%) [27]. While in 2020, Jiang and his team members studied 1,410 children with CHD. The total number of patients with abnormal urogenital systems was 104. The overall prevalence of CAKUT was 7.4%. In addition, they stated that there was no statistically significant difference for maternal age, sex, gestational age, and history of medication during pregnancy between the patients with CAKUT and those without CAKUT [10].

Conclusion

CAKUT is common among patients admitted into the cardiac PICU with

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CHD. CAKUT is associated with increased morbidity, length of PICU stay and poor outcome. Pelvi-abdominal ultrasonography screening is one of the gold standard investigations for screening of CAKUT. It is a reliable, available and cheap bedside tool. Proper maternal history taking, alongside with proper analysis of the PICU admission course may be a clue to increase the suspicion around the presence of CAKUT.

Recommendations

Further studies should be applied on large number of neonates, infants and children in order to detect the epidemiology and the risk factors for CAKUT in patients with CHD in Egypt. Pelvi-abdominal ultrasonography screening should be done routinely to all patients admitted with CHD to exclude the presence of CAKUT.

Study limitations

- This study included small number of patients in comparison to most of other studies.
- Our eight patients with abnormal ultrasonographic renal findings were non-syndromic by clinical appearance, but the genetic studies were not routinely investigated to be correlated with coexisting renal anomalies.

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Statements

Ethics approval and consent to participate: The local ethical committee permitted the study under the Helsinki declaration of Bioethics and its later amendments. Informed consent (written form) was obtained from all participants or their caregivers.

Consent for publication

Availability of data and material

"Not applicable", The author has indicated that the data and material are factual and genuine.

Conflict of interest

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