Original Article

The Association Between Markers of Inflammation and the Progression of Chronic Kidney Disease in Children with Congenital Anomalies of the Kidney and Urinary Tract (CAKUT).

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ABSTRACT

Introduction: Congenital anomalies of the kidney and urinary tract (CAKUT) are a leading cause of chronic kidney disease (CKD) in children. Despite the advancements in prenatal diagnosis and early management, the need for biomarkers for early prediction and diagnosis of CKD in those children is emerging.

Aimed of the study: To evaluate the efficacy of plasma Kidney injury molecule-1 (KIM-1) and tumor necrosis factor-alpha (TNF-α) in early prediction of CKD progression in children with CAKUT.

Methods: A cross-sectional controlled study included 60 children with CAKUT and CKD (stages 2, 3, and 4) and 60 healthy children as a control group. All included children were subjected to a comprehensive history taking, clinical examination, and investigation, including blood urea, serum creatinine, CBC, GFR calculation, KIM-1, and TNF-α plasma levels.

Results: TNF-α and KIM-1 levels were significantly higher in patients than controls ($p<0.001$ for both). Also, Kim-1 and TNF-α levels were significantly higher in the severe CKD group than in non-severe CKD ($p <0.001$ and 0.005, respectively). Both markers were significantly positively correlated to serum creatinine and GFR. The receiver operating characteristic analysis demonstrated that both TNF-α and KIM-1 could predict early CKD even prior to the increase in creatinine levels. Furthermore, they can also predict the progression of CKD when there are slight changes in creatinine levels.

Conclusions: TNF-α and KIM-1 could predict the progressiont of early CKD even prior to the increase in creatinine levels. They can also predict CKD progression when there are slight changes in creatinine levels.

Keywords: Congenital anomalies of the kidney and urinary tract, chronic kidney disease, TNF-a, KIM-1.

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INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) are a group of malformations resulting from alterations in the development of the kidney and/or urinary system [1]. CAKUT comprehends a broad spectrum of malformations, including kidney dysplasia, hypoplasia, agenesis, horseshoe kidneys, pelvi-ureteric junction obstruction (PUJO), vesicoureteric junction obstruction (VUJO), posterior urethral valve (PUV), and vesicoureteric reflux (VUR) [2, 3] CAKUT can manifest clinically with a wide range of severity, being symptomless up to CKD [4]. CAKUT, as a group of diseases, is prevalent in children and youths, and it is a primary cause of end-stage kidney disease (ESKD) in those age groups [5]. CKD progression can be influenced by variable factors including prematurity, gender, and attacks of pyelonephritis, the reduction in kidney size and nephron number, tubulointerstitial modifications, and remodeling of the collecting ducts epithelium [6]. Although CAKUT can be detected prenatally and treated surgically to eliminate obstructions, the varying severity and duration of these malformations often result in diverse levels of kidney damage. This damage can lead to proteinuria, hypertension, and, eventually, CKD [7]. CKD is defined by an enduring status of inflammation that can intensify as the disease advances [8]. There is a correlation between inflammatory markers and changes in glomerular filtration rate (GFR), as reported by previous studies [9]. Kidney injury molecule-1 (KIM-1) molecules have been reported to play a role in diagnosing renal function impairments and demonstrating the ongoing process of kidney damage [10]. Moreover, elevated levels of tumor necrosis factor-alpha (TNF-α) in the bloodstream were associated with deterioration of kidney function and a higher likelihood of illness and mortality in patients with CKD [11]. In this study we aimed to investigate the correlation between plasma levels of TNF alpha and KIM-1 and renal function in children with CAKUT.

METHODS

A cross-sectional, case-control study was conducted at the nephrology outpatient clinic from July 2023 to December 2023. The study included 120 children. They were divided into 2 groups: Group (1): 60 patients with chronic kidney disease and CAKUT. Group (2): 60 healthy children matched for age and sex as a control group. Diagnosis of CKD was based on the Kidney Disease Outcomes Quality Initiative (K/DOQI) [12]. The patient's group was further subdivided according to the stage of CKD into 3 groups: group 1, patients with CKD 2 (eGFR 90-60 ml/min/1.73 m^2), group 2; patients with CKD 3 (eGFR 60-30 ml/min/1.73 m^2), and group 3; patients with CKD 4 (eGFR 30-15 ml/min/1.73 m^2). Patients with CKD 2 and 3 were considered to have non-severe CKD and patients with CKD 4 were considered severe CKD.

The inclusion criterion was patients with CKD stages 2, 3, and 4 of both sexes aged less than 17 years at the time of presentation with the diagnosis of CAKUT. The exclusion criteria were patients with acute kidney injury, kidney transplant, immunotherapy in the past six months, infection during the last 3 months before enrollment in the study, and patients on dialysis. All included children

were subjected to detailed clinical evaluation. History taking (age, sex, original renal disease, age of onset of the disease, disease duration, antihypertension medication, history of other sibling affection with CAKUT. Clinical Examination: The anthropometric measurement included weight in kilograms (Kg) and height in centimeters (cm), weight for age (weight percentile), height for age (height percentile) and body mass index (BMI), Vital signs, local cardiac, chest, and abdominal examinations. Laboratory investigations:

Sample collection: Three ml of venous blood were withdrawn from each child. Two ml into plain tubes were centrifuged for quantitative electrolytes, urea, and creatinine measures. One ml was collected into EDTA tubes for the TNF-α and KIM-1 and centrifuged at 1600xg for 15 minutes at 4 ^{0} C. Collected samples were kept at -80 ^{0} C until the assay.

Statistical analysis

The data collected were analysed by the Statistical Package for the Social Sciences (SPSS version 20.0). Qualitative data are represented as numbers and percentages. The Chi x2 test is used to evaluate differences between groups based on the type of data. The quantitative data was represented by the mean ± standard deviation (SD), and the differences between groups were assessed using T-tests and a one-way analysis of variance (ANOVA). The Pearson correlation test assessed the correlations. The sensitivity, specificity, and 95% confidence interval (CI) of the cutoff values for the markers were determined using ROC curve analysis. A significance level of less than 0.05 was used to determine statistical significance.

Complete blood count (white blood cell count, red blood cell count, platelet count, hemoglobin, hematocrit), sodium, potassium, urea, and serum creatinine were assayed using routine biochemical methods, normalized GFR by DMSA and DTPA scan in patients and eGFR by Schwartz formula in controls **[13]**, TNF-α, and KIM-1 levels were measured using ELISA kits (Elbascience, Houston, Texas, USA). The local ethical committee approved the study, and informed consent was obtained from the caregivers of the included children.

RESULTS

In the patient's group, 40% were aged less than 2 years (range1-15 years), the male sex was (46/60, 76.7%), and prenatal diagnosis was reported in 30 % of patients. As regards the clinical data, short stature was reported in 50% of patients (< 3rd percentile). 43.3% of the patients were hypertensive (systolic pressure > 97th percentile for age and sex). The most frequent anomalies were posterior urethral valve (PUV) in 33.3%, pelvic-ureteric junction obstruction (PUJO) in 30%, neurogenic bladder in 15%, vesicoureteric reflux in 13.3%, and ureteric stricture in 8.3%. Bilateral kidney affection was reported in 32 (54%) of patients. Sixteen patients (26.6%) had CKD2, 19 (31.6%) had CKD3, and 25 (41.6%) had CKD4.

Comparison between patients and controls regarding clinical and laboratory data are shown in **Table 1**. The anthropometric measurements were significantly lower in cases than in controls ($p<0.05$). Patients' systolic and diastolic blood pressures were significantly higher than controls ($p<0.001$). Blood urea and serum creatinine were significantly higher in the

cases group, while the GFR was significantly lower in cases (p<0.001 for all). TNF-α and KIM-1 levels were significantly higher in patients than controls (p<0.001 for both).

Comparisons between the three CKD stage groups are shown in **Table 2.** KIM-1 levels were significantly higher in CKD4 than in CKD2 and CKD3 groups (p<0.001), with no significant differences between CKD2 and CKD3 groups. TNF-α levels were significantly higher in CKD4 than in CKD2 (p; 0.02) without significant differences between the other groups. The comparison between patients with severe and non-severe CKD showed that the severe CKD group had significantly higher serum levels of Kim-1 (p<0.001) and TNF- α (p; 0.005) compared to the non-severe CKD group **Table 3**. Both KIM-1 and TNF- α were significantly positively correlated to s.creatinine (r;0.3, p; 0.02 and r; 0,45, p: <0.001 respectively), and the two markers were negatively correlated to GFR (r; -0.4, p; 0.001 for KIM-1 and r; -0.3, p: 0.007 for TNF- α.).

The ROC analysis for the two markers showed that to discriminate between cases with early CKD and controls, a KIM-1 cutoff value of > 9.8 pg/ml has 100% sensitivity, 96.7% specificity, and AUC of 0.98, and TNF- α cutoff value of > 730 pg/ml has 100% sensitivity, 93.3 % specificity and AUC of 0.92 with significantly higher predictive value compared to serum creatinine (p-value 0.03 and 0.04 respectively at a creatinine cutoff 0.34 mg/dl)) **Figure 1**. Also, The ROC analysis for the two markers showed that to discriminate between cases with severe and non-severe CKD, a KIM-1 cutoff value of > 16.25 pg/ml has 98.67% sensitivity, 77.2% specificity and AUC of 0.91, and a TNF-α cutoff value of >927 pg/ml has 81.7% sensitivity, 71% specificity and AUC of 0.81. Both were comparable to creatinine at a cutoff value of 0.77 mg/dl (p>0.05) **Figure 2.**

Table 1: Comparison between patients and controls regarding clinical and laboratory data

	Controls (n=60)	Cases (n=60)	p
Age (years)	6.16± 4.53	5.02± 4.22	0.16
Weight (kg)	20.48± 9.06	14.43± 6.66	<0.001
Weight percentile	53.67± 32.21	23.57± 15.69	<0.001
Height (cm)	112.33± 23.60	102.47±19.62	0.01
Height percentile	55.53± 36.07	37.40± 21.83	0.01
BMI (kg/m^2)	15.19± 2.68	13.49 ±3.90	0.01
Systolic pressure (mmHg)	94.00± 15.75	102.69±11.61	<0.001
Diastolic pressure (mmHg)	57.83±12.87	66.03±11.19	<0.001
Hemoglobin (g/dl)	10.03±1.76	9.51±1.38	0.07
Leucocytes ($x10^3$ cell)	9.52± 5.58	8.94± 3.70	0.50
Platelets ($x10^3$ cell)	394.93± 105.41	268.30± 89.83	<0.001
Sodium (mEq/L)	139.47± 5.98	138.03± 5.89	0.19
Potassium (mEq/L)	4.47± 0.63	4.66± 0.85	0.17
Urea (mg/dl)	31.33± 12.92	84.53± 49.81	<0.001
S. creatinine (mg/dl)	0.39± 0.09	1.39± 1.07	<0.001
GFR ($ml/min/1.73m^2$) Glomerular Filtration Rate	122.82± 29.12	44.89± 26.62	<0.001
KIM1 (pg/ml) Kidney injury molecule -1	2.31±0.62	34.64±22.18	<0.001
TNF-α (pg/ml) Tumor necrosis factor-alpha	735.33± 340.26	1434.62±1002.76	<0.001

p-value < 0.05 is considered significant

Table 2: Comparisons between the three chronic kidney disease (CKD) stage groups

	CKD2 (n=17)	CKD3 (n-19)	CKD4 (n=24)	p
Age (years)	2.47± 1.32	5.58± 2.94	6.04± 3.24	* 0.08 ** 0.02 *** 0.98
Weight percentile	16.19 ± 10.20	16.68± 5.02	18.92± 7.37	* 0.83 ** 0.62 *** 0.99
Height percentile	47.50± 14.62	44.42± 14.65	5.29± 3.20	* 0.99 ** <0.001 *** 0.01
BMI (kg/m^2)	12.49± 3.38	13.83± 5.42	13.94± 2.65	* 0.67 ** 0.57 *** 0.99
Systolic pressure (mmHg)	98.53± 9.81	96.18± 6.26	109.83± 12.14	* 0.87 ** <0.001 *** <0.001
Diastolic pressure (mmHg)	60.59± 8.99	59.41± 10.88	73.33± 8.43	* 0.98 ** <0.001 *** <0.001
Hemoglobin (g/dl)	9.23± 1.31	9.33± 1.60	9.80±1.26	* 0.99 ** 0.49 *** 0.62
Sodium (mEq/l)	140.82± 4.10	139.26± 3.28	135.58± 7.67	* 0.80 ** 0.02 *** 0.11
Potassium (mEq/l)	4.17± 0.65	4.73± 0.91	4.95± 0.79	* 0.12 ** 0.01 *** 0.76
Urea (mg/dl)	61.77± 24.05	63.16± 23.02	117.33± 60.71	* 10.99 ** <0.001 *** <0.001
Creatinine (mg/dl)	0.52± 0.11	1.03± 0.31	2.31± 1.13	* 0.12 ** <0.001 *** <0.001
KIM1 (pg/ml) Kidney injury molecule -1	26.42± 6.14	24.07± 5.92	50.04± 28.09	* 0.97 ** <0.001 *** <0.001
TNF-α (pg/ml) Tumor necrosis factor-alpha	815.50± 395.24	1390.45± 103.34	1871.00± 106.97	* 0.20 ** <0.001 *** 0.27

* Comparison between CKD2 and CKD3 ** Comparison between CKD2 and CKD4
*** Comparison between CKD3 and CKD4 p-value < 0.05 is considered significant

Table 3 : Comparison between patients with severe and non-severe CKD.

	Severe CKD (n=24)	Non- severe CKD (n=36)	p
Hb (g/dl)	9.80± 1.26	9.32± 1.44	0.19
WBCs (x10^3 cell)	9.42± 2.21	8.62± 4.43	0.42
Platelets (x10^3 cell)	268.00± 78.78	268.50± 97.59	0.98
Sodium (mEq/l)	135.58± 7.67	139.67± 3.61	0.01
Potassium (mEq/l)	4.95± 0.79	4.47± 0.84	0.03
Urea (mg/dl)	117.33± 60.71	62.67± 23.03	<0.001
Creatinine (mg/dl)	2.31± 1.13	0.79± 0.36	<0.001
GFR (ml/min/1.73m^2) Glomerular Filtration Rate	22.07± 5.90	60.11± 24.00	<0.001
KIM1 (pg/ml) Kidney injury molecule -1	50.04± 28.09	24.13± 5.71	<0.001
TNF-α (pg/ml) Tumor necrosis factor-alpha	1871.00± 106.97	1143.69± 158.07	0.01

p-value < 0.05 is considered significant

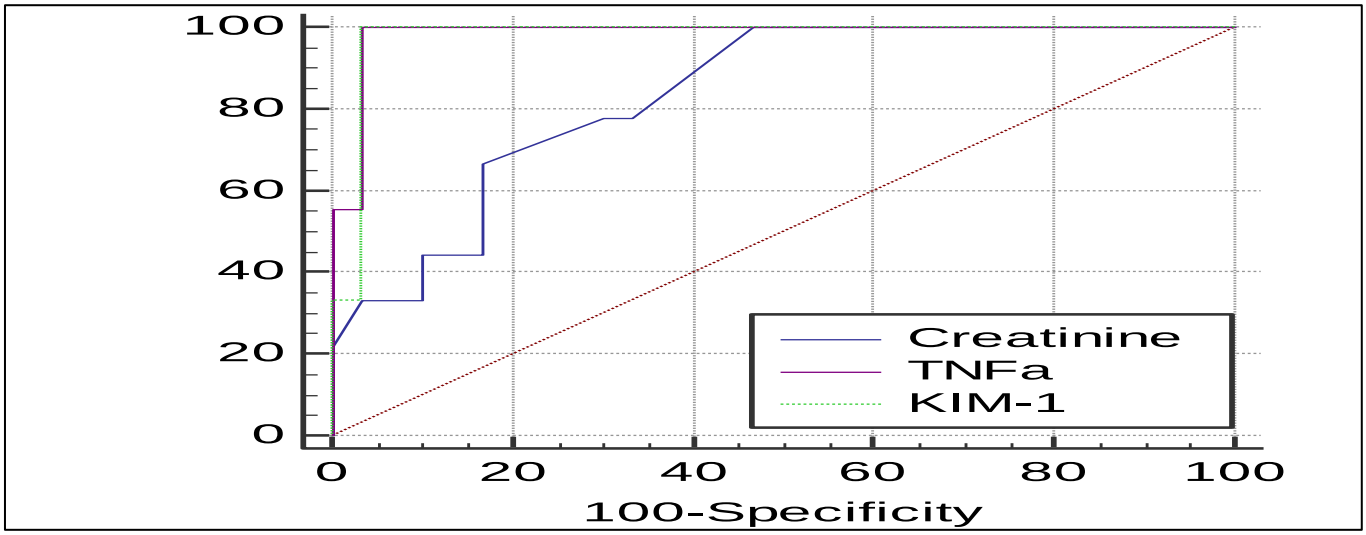

Figure 1: The ROC for creatinine, TNF-a and KIM-1 to discriminate between cases with early CKD and controls

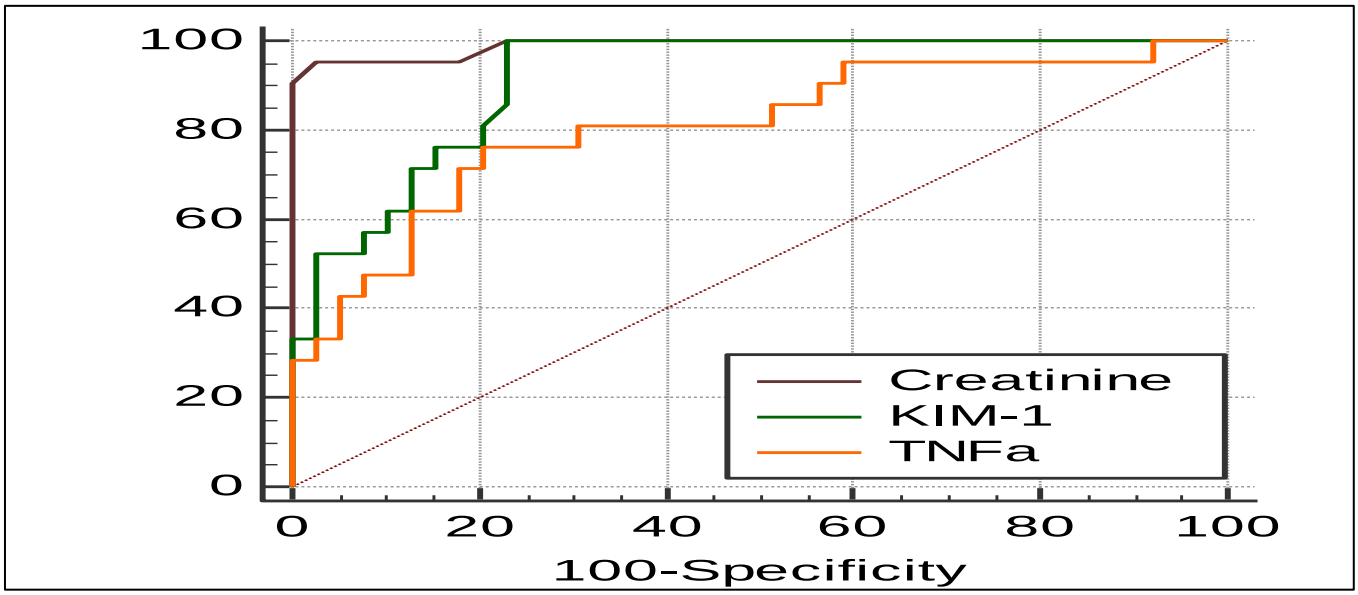

Figure 2: The ROC for creatinine, TNF-a and KIM-1 to discriminate between cases with severe and non-severe CKD.

DISCUSSION

CAKUTs are a common etiology of CKD in pediatric age groups, accounting for 53% of cases of CKD in children [14]. In the meta-analysis conducted by Shahdadi et al., a total of 13 studies carried out on 3,596 Iranian children, CAKUT reported in 37% the main cause the overall main cause of chronic kidney disease in stages 1–4 (CKD) was CAKUT (37%) and in stage 5 (ESKD), 40.82% were CAKUT [15]. Similarly, the ItalKid Project [16]and the ESCAPE trial [17], as well as a Japanese CKD survey in children, had documented the predominance of CAKUT as a cause of CKD [18]. In our cohort, the male sex was predominant. Similar findings were reported by Tain et al., who found that 66 % of infants with CAKUT were males, and male sex was an independent risk factor for CAKUT [19].

Half of our patients showed linear growth retardation. Approximately 35% of children with CKD had heights below the third percentile or median height standard

deviation scores (HtSDS) under 1.88, according to the 2006 North American Pediatric Transplant Cooperative Study involving more than 5000 children [20]. Assumed that 30% of all growth takes place in the first two years of life, infants with CKD are at a high risk of experiencing significant growth retardation, which might negatively affect final height. Children with CKD have development delays for various reasons, including metabolic acidosis, renal osteodystrophy, anomalies of the growth hormone-IGF-1 axis, and poor nutrition [21].

Previous studies showed that about 50% of children with CAKUT have lower urinary abnormalities, which include vesicoureteral reflux (25%), ureteropelvic junction blockage (11%), and ureterovesical junction obstruction (11%) [22]. In our study, The most frequent anomalies were posterior urethral valve (PUV) in 33.3%, pelvic-ureteric junction obstruction (PUJO) in 30%, and vesicoureteric reflux in 13.3%. CKD is a major morbidity in children with CAKUT; in our study, 41.6% of our patients had CKD4 at enrollment. It is well-known that inflammation can affect CKD progression and outcome [13], but the linkage between the initiation of the disease and inflammation is still under argument. Like other chronic diseases, CKD is associated with low-grade chronic inflammation, which can adversely influence the progression of CKD and uremia-associated complications [9].

Regarding TNF-α, TNF-α levels were significantly higher in the patient's group than the controls, and they were significantly higher in CKD4 than in CKD2 without significant differences between CKD2 and CKD3. The levels of TNF-α were significantly correlated to serum creatinine and GFR. These results align with those of earlier major epidemiological studies, which discovered that patients with CKD had greater TNF-alpha levels, and it was higher in participants with lower eGFR levels [11, 23]. Also, Liu et al., in a study, included a total of 78 CKD cases and allocated them into three groups according to the CKD stage: CKD stage 1&2 group, CKD stage 3&4 group, and CKD stage 5 group showed that the severity of renal inflammation was correlated to inflammatory factors including TNF-α [24].

Similarly, Amdur et al. showed that plasma TNF-α levels were significantly associated with the deterioration of kidney function in a large cohort of CKD [8]. A more recent study [25] that included 42 children with CKD with a mean age of 10.7 years and 21 healthy children as a control group reported that TNF-a was significantly higher in the CKD group compared to controls. Nonetheless, no correlations to most of the parameters used for CKD estimation, including eGFR, were reported. As a result, they concluded that its utility in the early diagnosis of kidney impairment in children had not been established. This divergence in results may be related to the different underlying causes of CKD in their group (only 45% were CAKUT), and 23% of their patients were on renal replacement therapy, mainly peritoneal dialysis (PD). In their study, TNF-a and s.creatinine was measured in an early morning sample.

As patients on chronic ambulatory PD undergo night dwells, their morning creatinine levels are expected to be low compared to their CKD stage, explaining the absence of correlations between TNF-a and both creatinine and eGFR. Although our study could not establish causality

from the observed relationships as an inflammatory biomarker, TNF-a may have been associated with kidney disease simply due to decreased renal clearance; the study by Gamrot and his colleagues reported significantly higher serum and urinary levels of TNF-a in children with CKD compared to controls [25].

While monocytes, macrophages, and T cells are the primary producers of TNF-a, TNF-a can also be produced by renal glomerular, tubular, and endothelial cells. TNF- stimulates the production of reactive oxygen species (ROS), increases albumin leakage, and induces cytotoxicity, apoptosis, and necrosis, and it is involved in the recruitment of monocytes and macrophages, hemodynamic alterations that leads to reduction of GFR, and the alteration of endothelial permeability [26].

In an animal module, kidney obstruction increased tissue TNF-α levels and TNF-α protein production, and apoptosis of renal tubular cell. In contrast, neutralization of TNF-a led to significant reduction of renal tubular cell apopstosis induced by obstruction. TNF- drives obstruction-induced renal tubular cell apoptosis and proapoptotic signaling, and TNF- neutralization is identified as a viable treatment strategy for ameliorating obstruction-induced renal injury [27].

In this study, we reported that KIM-1 levels were significantly higher in cases than controls. Also, we found that KIM-1 levels were significantly higher in advanced CKD stage 4 compared to CKD stages 2 and 3, and KIM-1 levels were significantly correlated with both s. creatinine and GFR. Prior research conducted on patients with CKD) [28] revealed that the levels of KIM-1 were significantly higher in patients with CKD compared to healthy controls. In addition, Schmidt et al. [29] conducted a study where they measured the levels of KIM-1 in the serum of 524 adult patients with CKD. They reported that higher levels of KIM-1 were linked to more advanced stages of CKD.

Research conducted on adults with diabetes has shown that measuring plasma KIM-1 levels can predict the likelihood of developing or worsening CKD [30, 31]. Two studies examining plasma and urine KIM-1 levels found that elevated plasma KIM-1, but not urinary KIM-1, was linked to a higher prospect of early renal function deterioration in patients with type 1 and type 2 diabetes who do not have CKD [30, 32]. Patients with early and progressive diabetic kidney disease from the ACCORD and VA NEPHRON-D clinical studies showed a correlation between elevated levels of plasma KIM-1 and a progressive decline in kidney function over time [33]. Previous studies have found a correlation between elevated plasma levels of KIM-1 and the occurrence of chronic kidney disease (CKD) in healthy individuals [31], as well as the advancement to renal failure in individuals with moderate to severe CKD [34].

A possible reason for the discrepancy in predictive significance between urine and plasma KIM-1 is that urinary KIM-1 can indicate the severity of acute tubular damage and the synthesis of KIM-1 in response to injury. On the other hand, plasma KIM-1 may more accurately reflect the cumulative effect of injury over time and ongoing production. It is released into the bloodstream when there is a disruption in the polarity of tubular cells [31, 35]. Studies using rodent models of chronic kidney disease (CKD) have demonstrated that continuous overexpression of KIM-1 leads to the formation of fibrosis, which is

accompanied by macrophage chemotaxis mediated by monocyte KIM-1, being a transmembrane molecule, cannot be detected in the tubular cells of individuals with normal kidney function.

Patients with impaired kidney function, characterized by notable differentiation and proliferation of tubular epithelial cells, exhibit elevated levels of KIM-1 in both urine and plasma samples. For the early identification of renal disease, serum creatinine is not very accurate or reliable. Therefore, it is essential to use appropriate serum indicators for the diagnosis and prognosis of CKD [37]. The receiver operating characteristic (ROC) analysis demonstrated that both TNF-α and KIM-1 could predict the progression of early CKD even prior to the increase in creatinine levels. Furthermore, they can also predict the progression of CKD when there are slight changes in creatinine levels.

LIMITATIONS OF THE STUDY

Relatively small sample size due to the exclusion of cases with normal GFR and patients with CKD5 from the study**.**

RECOMMENDATIONS

Screening for the progression of CKD in patients with CAKUT using inflammatory markers can help in early management and the prevention of progression even before the rising of creatinine.

CONCLUSION

This study found a strong correlation between the levels of TNF-α and KIM-1 in the blood plasma and the occurrence of CKD in children with CAKUT. Furthermore, higher levels of these biomarkers were correlated with a greater drop-in glomerular filtration rate and the progression of more severe forms of CKD.

ABBREVIATIONS

CAKUT	Congenital anomalies of the kidney and urinary tract
CKD	Chronic kidney disease
GFR	Glomerular filtration rate
KIM-1	Kidney injury molecule -1
PUJO	Pelvic-ureteric junction obstruction
PUV	Posterior urethral valve
TNF-a	Tumor necrosis factor-alpha
VUJO	Vesicoureteric junction obstruction
VUR	Vesicoureteric reflux

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AUTHORS' CONTRIBUTIONS

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STATEMENTS

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Beni-Suef University, Faculty of Medicine and the ethics code was FWA00015574 FMBSUREC /09072023/AHMED Also, written informed consent was obtained from the parents of the participating children.

Consent for publication

The contents and material of the manuscript have not been previously reported at any length or are being considered for publishing elsewhere.

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