Egyptian Journal of Medical Research (EJMR)

Value Of Serum Procalcitonin As A Diagnostic Biomarker Of Infection In Children With Chronic Kidney Disease

Osama Ezzat Botrous [a], *Amna Gouda Mabrouk* [b] *and Gaber Ibrahim Awad* [b]

[a] Pediatrics department, Faculty of Medicine, Beni-Suef University, Egypt

[b] Pediatrics department, Faculty of Medicine, Beni-Suef University, Egypt

Abstract:

Introduction: Serum procalcitonin (PCT) levels are known to be low in healthy individuals in healthy subjects but are increased in patients with a severe bacterial infection. It has not been extensively studied in children with chronic kidney disease (CKD).

Patient and method: The present study was conducted on 60 chronic kidney disease pediatric patients. The patients were recruited from Beni-suef university hospital department of pediatrics. They were divided into 2 groups, group (I)(case) include 30 pediatric patients of chronic kidney disease with proven infection and the second group(II) (control) include 30 chronic kidney disease pediatric patients apparently healthy (without infections). Procalcitonin levels were measured by ELISA. **Results**: Children with proven infections had a significantly higher PCT (0.87±0.21ng/ml) than those without (0.50±0.18ng/ml), p = 0.04. The ideal cutoff value derived for serum PCT was 0.63ng/ml. This threshold value established a sensitivity of 93.3% and a specificity of 80.0%.

Conclusion: This study indicates that significantly increased PCT concentration is a promising predictor of systemic bacterial infection in children with CKD, with good sensitivity and specificity. This study proposes that serum PCT is a convenient index of infection in CKD children at a cutoff value of 0.63ng/ml.

Keywords: Chronic kidney disease, children, infection, procalcitonin.

1. Introduction:

Chronic kidney disease (CKD) is a significant public health dilemma with an advanced requirement for dialysis either hemodialysis (HD) or peritoneal dialysis every year [1]. The increased risk of infection in CKD patients has been demonstrated [2] especially in those treated with chronic HD [3].

Risk markers that possibly mark this susceptibility to infection are plentiful, including coexisting illnesses such as immunosuppressive therapy for the underlying kidney disease, uremia-induced leukocyte dysfunction, vaccine hypo-responsiveness, malnutrition, bloodstream infections fundamentally concerning vascular (fistula or catheters) access [4] and hemodialysis with frequent disturbance of the skin barrier. For all these reasons, CKD may be considered as a condition of acquired immunodeficiency [5].

Moreover, it has been reported that at the moment of infection, CKD patients had a much greater risk of mortality than healthy individuals [6], due to which infection is the second main cause of mortality after cardiovascular diseases. Furthermore, infectious disease is a leading reason for intensive care unit (ICU) admittance and accounts for 15% to 25% of overall ICU admittance in CKD patients [7].

Clinical and laboratory signs of systemic infection, including hypo/or hyperthermia, apnea or tachypnea, tachycardia and increased white blood cell counts, are critical. However, their application is restricted by inferior specificity and peculiarity for the diagnosis of sepsis, as seriously sick patients often have the systemic inflammatory response syndrome (SIRS) but no infection [8].

Some inflammatory parameters, such as leukocyte cell count, cytokines (TNF-α, IL-1β, or IL-6) and C-reactive protein (CRP), have been applied for the diagnosis of infection and inflammation, but their deficiency of specificity has drawn attention to the need for more specific laboratory investigations [9].

Procalcitonin (PCT), the precursor protein of calcitonin, is a polypeptide of 116 amino acids (MW13 kDa) which has been reported to be able to accurately distinguish bacterial from nonbacterial infections and other inflammation conditions [10].

In contrast to C-reactive protein, PCT secretion is inhibited by interferon γ (IFN-γ), a cytokine which is manufactured during viral infections. It has been confirmed as helpful in distinguishing complications due to bacterial infections [11]. Serum PCT level is rising at 3 to 6 hs following bacterial infection, but is not in autoimmune disease, non-infectious inflammatory responses, local infection, viral infection or sepsis. So, it might seem that PCT measurement has the ability to raise the certainty of the diagnosis of a bacterial infection greater than measuring other infection parameters, such as leukocyte counts or CRP [12].

Procalcitonin has not been widely studied in children with CKD or renal transplant (RTx). The scarce presently obtainable studies are either comparatively small in sample size or use unrepresentative individuals [13]. Therefore, the comparative advantage of PCT testing in children with chronic kidney disease is not certain [14].

2. Patients and Methods:

This study was conducted from January 2019 to April 2020, cases were recruited from pediatric department of Beni-Suef University hospital. It was carried on 30 children aged from 2 years to 13 years suffering from chronic kidney disease (with suspected infection detected initially by clinical symptoms) and a control group that included 30 patients aged from 2 years to 13 years with chronic kidney disease but without suspicion of having infection.

Study design:

A prospective case control study was adopted to fulfill the purpose of the study in pediatric department in Beni-suef university hospital including children with chronic kidney disease with a strong clinical suspicion of infection.

Inclusion criteria:

1. Age all pediatric groups suffering from chronic kidney disease (2-13 years).
2. Sex both genders will be included.
3. Children presented by fever over 38°C, with bacterial infection as bacterial pneumonia (with clinical signs and symptoms suggestive of lower respiratory infections fever, cough with or without sputum, chest pain, dyspnea, and altered breath sounds on auscultation and/or the presence of an infiltrate on chest X-ray), urinary tract infection (with clinical signs and symptoms of UTI as dysuria ,urgency ,frequency and change color of urine), vascular access infection (with redness, hotness, and tenderness), enterocolitis (diarrhea, vomiting, high grade fever) and meningitis (disturbed consciousness, vomiting, neck rigidity) .
4. control group that included 30 patients aged from 2 years to 13 years with chronic kidney disease but without suspicion of having infection.

Exclusion criteria

1- Known viral infections as (measles, chicken pox).

2- Other chronic illness as (Tuberculosis and Malignancy).

2.2 All patients were subjected to:

1. Detailed history taking with stress on fever, any complaint as cough, diarrhea, convulsion, vomiting, dysuria and abdominal pain.
2. Thorough clinical examination including general examinations e.g vital signs, anthropometric measurements, local cardiac, chest and abdominal examinations.
3. Investigations which included:

a) Routine laboratory investigations:

• Blood analysis such as: Complete Blood Count (CBC), kidney function tests, electrolytes

• Urine analysis to detect pus cells, hematuria

• Markers of infections as acute phase reactants such as: C- Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR).

b) Specific laboratory investigation:

• Procalcitonin level tested by Enzyme-Linked Immunosorbent Assay (ELISA).

c) Radiological investigation:

Chest X - ray for pneumonic patients, ultrasound examinations, or computed tomography scans were recommended when a clinically based infection was suspected.

-The total leukocytic count and platelet counts were measured on an automated counter.

- CRP:- Blood was collected into two 3 ml lithium-heparin coated tubes for basic clinical chemistry tests including CRP. serum was obtained by centrifugation of the blood at 4 C◦ with 2000 rpm for 15 minutes after which the serum was frozen at -80 C° until measurements took place. CRP was measured with a lower detection limit of 6 mg/L.

- Procalcitonin:- was measured using the PCT ELISA assay (Bio Vendor R&D, Germany). The normal range was defined as 0–0.2 ng/ml. For the analysis, we used cutoff value of 0.63 ng/ml.

Biochemical laboratory parameters were measured by an automatic biochemistry analyzer.

Statistical methodology

• Analysis of data was done by IBM computer using SPSS (statistical program for social science) as follows;

- Description of quantitative variables as mean, SD and range.
- Description of qualitative variables as number and percentage.
- Unpaired t-test was used to compare quantitative variables, in parametric data (SD < 50 % mean)

• P value > 0.05 insignificant
• P < 0.05 significant
• P < 0.01 highly significant [20].

3. Results:

The present study included 60 of children suffering from chronic kidney disease 3 of them were diagnosed to have pneumonia (clinically, laboratory and radiologically), 25 of them were dignosed to have urinary tract infection (clinically, laboratory), 2 of them were diagnosed to have enterocolitis (clinically, laboratory), and 30 matched clinically have no signs or symptoms of infection and they were studied as control group.

Table (1): Demographic characteristics among the studied groups

Variables		Confiremd infection (N=30)	No onfirmed infection (N=30)	P-value
Age (years)	**Mean±SD**	9.2±2.3	9.9±2.3	^0.289
	Range	5.0–13.0	3.0–13.0	
Sex, (n, %)	**Male**	22 (73.3%)	23 (76.7%)	#0.766
	Female	8 (26.7%)	7 (23.3%)	
BMI (kg/m^2)	**Mean±SD**	21.1±2.7	21.5±2.4	^0.537
	Range	16.7–25.6	17.3–26.7	
Duration of renal illness (years)	**Mean±SD**	4.6±2.9	4.1±2.7	^0.435
	Range	0.5–11.0	0.5–11.0	
Consanguiniy, (n, %)		12 (40.0%)	10 (33.3%)	#0.592

Table (1) shows that: No significant differences between the studied groups regarding demographic characteristics.

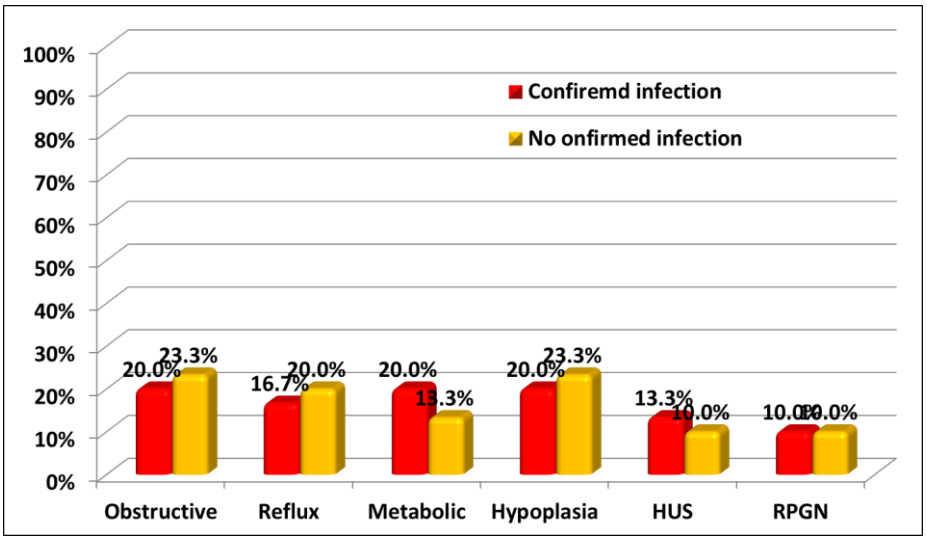

Figure (1): Causes of renal disease among the studied groups

congenital disorders, metabolic and Glomerulonephritis were the most prominent causes

Table (2): Vital data among the studied groups

Variables		Confiremd infection (N=30)	No onfirmed infection (N=30)	P-value
SBP (mmHg)	**Mean±SD**	107.9±5.6	110.2±6.1	^0.139
	Range	94.0–118.0	103.0–122.0	
DBP (mmHg)	**Mean±SD**	70.9±4.2	72.5±4.5	^0.168
	Range	62.0–77.0	67.0–83.0	
Temperature °C	**Mean±SD**	39.4±0.5	36.9±0.2	**<0.001***
	Range	38.1–40.2	36.6–37.2	
Respiratory Rate (cycle/min)	**Mean±SD**	19.6±4.0	17.5±1.0	**0.006***
	Range	16.0–35.0	16.0–20.0	
Heart Rate (beat/min)	**Mean±SD**	98.0±5.0	95.8±5.5	**0.116***
	Range	91.0–115.0	80.0–104.0	

^Independent t-test.

Table (2) shows that: **Temprature, respiratory rate and heart rate** were significantly higher in confirmed infection group.

Table (3): Laboratory findings among the studied groups

Variables		Confiremd infection (N=30)	No onfirmed infection (N=30)	P-value
Hb (gm/dl)	**Mean±SD**	11.6±0.8	11.7±0.9	0.901
	Range	10.3–13.8	10.1–13.5	
RBCs (cells/mm3)	**Mean±SD**	3.8±0.3	3.8±0.3	0.927
	Range	3.3–4.4	3.3–4.3	
Platelets (cells/mm3)	**Mean±SD**	248.0±43.8	262.7±37.3	0.166
	Range	169.0–342.0	182.0–366.0	
Lymphocytes (cells/mm3)	**Mean±SD**	4.8±0.9	3.5±0.4	**<0.001***
	Range	3.6–7.4	2.8–4.2	

Granulocytes (cells/mm3)	**Mean±SD**	2.1±1.1	2.2±1.3	0.847
	Range	0.2–4.1	0.2–4.4	
TLC ($x10^3$/mL)	**Mean±SD**	7.5±1.6	6.2±1.7	**0.003***
	Range	4.8–11.0	3.1–9.6	
CRP (mg/L)	**Mean±SD**	29.7±14.3	12.9±10.3	**<0.001 ***
	Range	3.0–60.0	0.0–١٢.0	
Procalcitonin (ng/mL)	**Mean±SD**	0.87±0.21	0.50±0.18	**<0.001 ***
	Range	0.57–1.42	0.18–0.79	

^Independent t-test. *Significant

Table (3) shows that: **TLC, Granulocytes, , CRP and procalcitonin** were significantly higher in cases with confirmed infection.

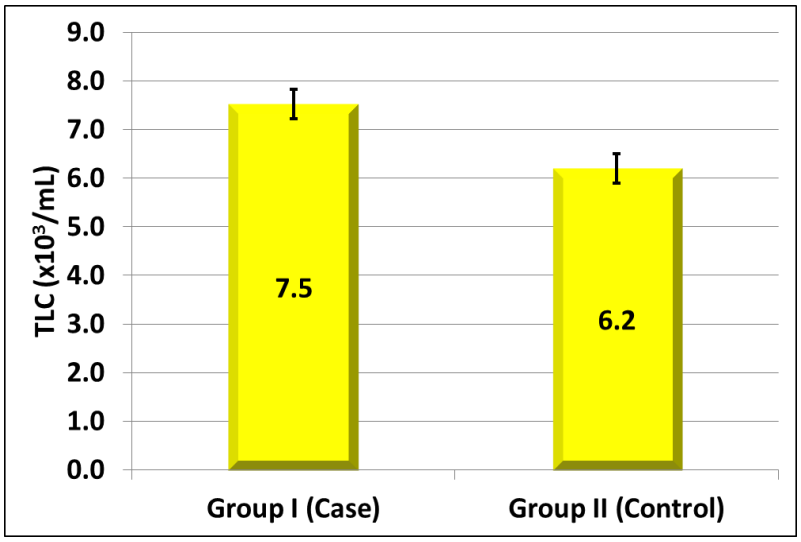

Figure (2): TLC among the studied groups

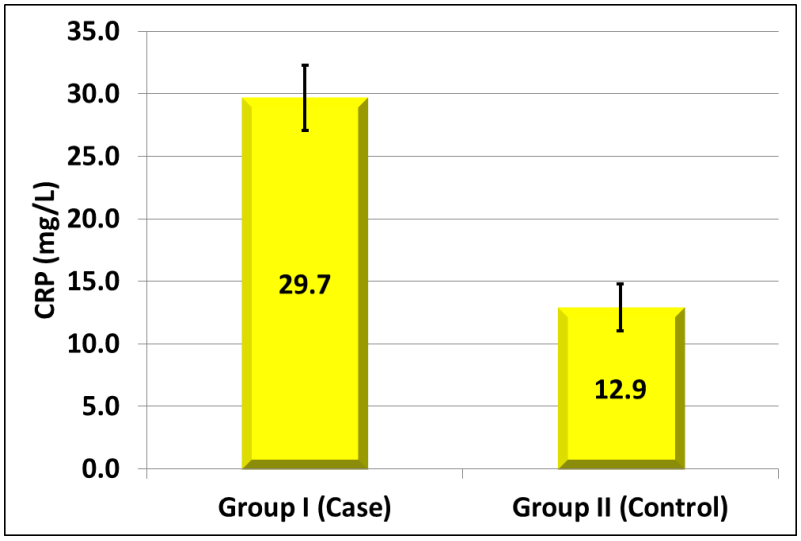

Figure (3): CRP among the studied groups

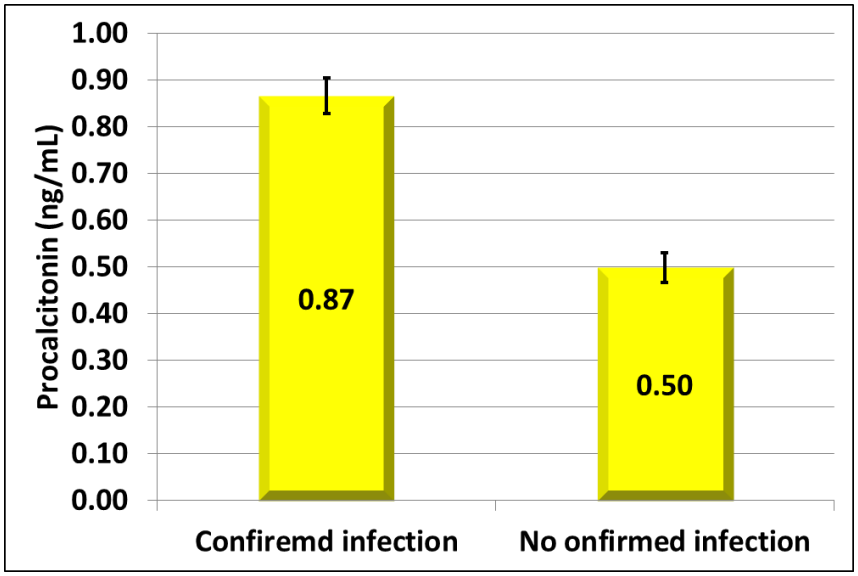

Figure (4): Procalcitonin among the studied groups

Table (4): Correlations of laboratory findings among the studied groups

Variable	Confiremd infection (N=30)		No onfirmed infection (N=30)	
	r	P-value	r	P-value
Procaclitonin				
Age	0.303	0.104	-0.102	0.591
BMI	-0.084	0.659	-0.323	0.082
Duration	0.166	0.379	-0.002	0.992
SBP	0.191	0.311	-0.121	0.526
DBP	0.135	0.476	0.111	0.560
TLC	0.502	**0.005***	0.612	**<0.001***
CRP	0.391	**0.033***	0.408	**0.025***
TLC				
Age	-0.040	0.835	-0.088	0.646
BMI	0.088	0.642	-0.179	0.343
Duration	0.004	0.982	-0.024	0.901
SBP	0.414	0.123	0.056	0.770
DBP	0.025	0.896	-0.076	0.689
CRP	0.594	**0.001***	0.517	**0.003***
CRP				

Age	0.072	0.706	-0.034	0.858
BMI	0.128	0.501	-0.199	0.292
Duration	-0.048	0.802	0.013	0.947
SBP	0.161	0.396	0.322	0.082
DBP	0.094	0.620	0.071	0.708

Pearson correlation. r: Correlation coefficient. *Significant

Table (4) shows that: There were significant positive correlations between **TLC, CRP and procalcitonin** in both study groups.

Table (5): Diagnostic performance of laboratory finding in diagnosing confirmed infection

Factors	AUC	SE	P-vale	95% CI	Cut off
TLC	0.713	0.066	**0.005***	0.584−0.843	≥7.3
CRP	0.821	0.054	**<0.001***	0.715−0.926	≥12.0
Procalcitonin	0.919	0.033	**<0.001***	0.854−0.984	≥0.63

AUC: Area under curve, SE: Standard error, CI: Confidence interval, *significant

Table (5): **Procalcitonin** had highest significant diagnostic performance in diagnosing confirmed infection.

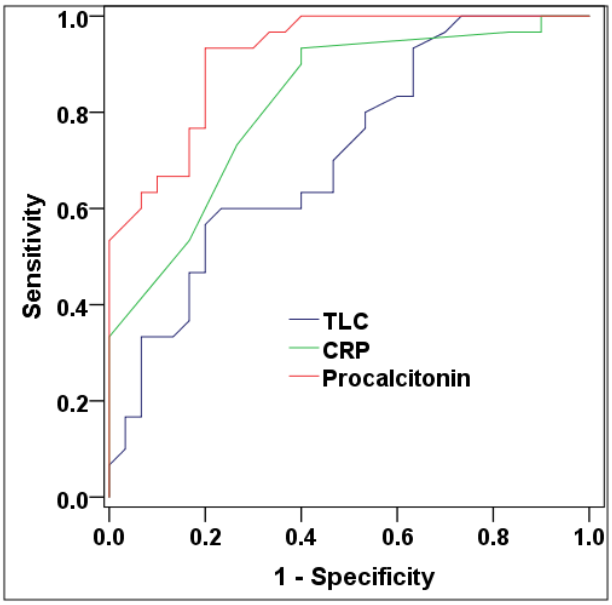

Figure (4): ROC curve for laboratory finding in diagnosing confirmed infection

Procalcitonin had highest significant diagnostic performance in diagnosing confirmed infection.

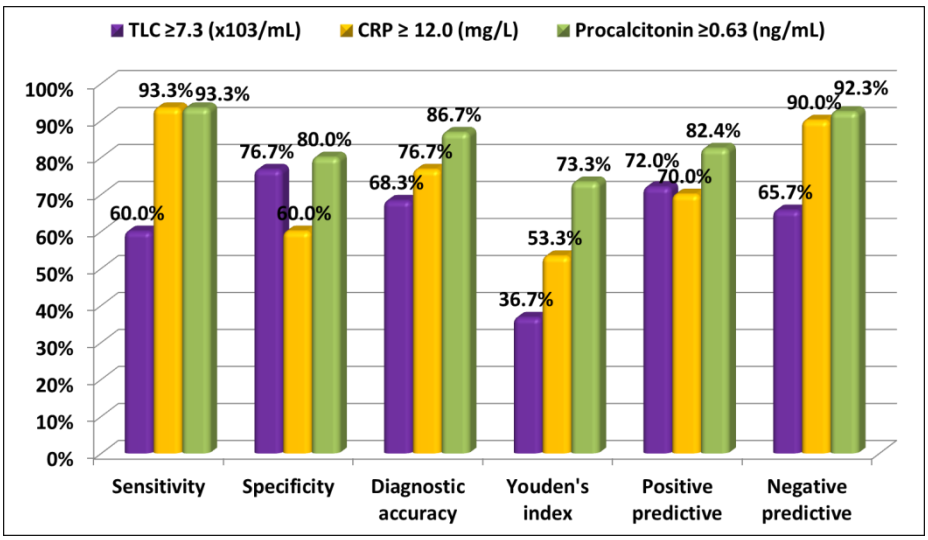

Figure (5): Diagnostic characteristics of laboratory cutoff points in diagnosing confirmed infection

4. Discussion:

Bacterial infections are a major cause of mortality in patients with chronic kidney disease as these patients are often clinically compromised [15]. Therefore, it is important to diagnose bacterial infection at an early stage to improve prognosis, The early initiation of antibiotic therapy has a major impact on the clinical outcome of these patients [16].

There is a dramatic increase in antibiotic resistance which emerged without the prospect of development of novel classes of antimicrobial agents. Therefore, reduction of the unnecessary use of antibiotics in mandatory [17]. Currently applied laboratory parameters of infection can be misleaded in these patients because of uremia Some of these parameters may be non-specifically decreased, such as white blood cell (WBC) count, and others may be nonspecifically increased, such as erythrocyte sedimentation rate, C-reactive protein (CRP), or other acute-phase proteins [18]. As a consequence, a multitude of biomarkers gained a lot of attention in diagnosis of bacterial infections. Among these, CRP and PCT which have found their way into daily practice. Bacterial infections caused by various classes of microorganisms are characterized by different concentrations of PCT and CRP [19].

If PCT can be used as a primary marker for bacterial infections in patients with chronic kidney disease, these infections can be diagnosed and treated early [20].

Our study aims to assess the value of measuring procalcitonin as a diagnostic marker for early diagnosis of bacterial infections in patients with chronic kidney disease based on the hypothesis that PCT serves as a good diagnostic marker for diagnosis of bacterial infections.

Therefore, this study was conducted on 60 child with chronic kidney disease who were further subdivided into: group (I), aged from 2 years to 13 years suffering from chronic kidney disease with strong clinical suspicion to have infection. and a control group (II) that included 30 patients aged from 2 years to 13 years with chronic kidney disease but without suspicion of having an infection.

Our study revealed that there is no significant difference in age between group (I) and group (II), This goes with Jamro et al., (2003) [21] who found that the age of children who have chronic kidney disease attending children hospital, Chandka Medical College ranged between 2-15 years either have infections or not.

Obstructive uropathy and Glomerulonephritis were the most prominent disease in our study, This is in contrast to (Engel et al., 2011) [22] who found that The most common identifiable cause of CKD was glomerular disease. Other studies as (Mitsnefes, 2003) [23] found that focal segmental glomeriolosclerosis was major cause of chronic renal failure among children.

During the study period, 30 children (Group I) had proven infections with the following breakdown: 3 children with pneumonia (10.0%), 25 with urinary tract infection (83.33%), and 2 with enterocolitis (6.66%).

There were 10.0%(3 cases) of patients of group (I) presented mostly by: cough (100%), crepitation ,high grade fever due to bacterial pneumonia, and there were 6.66% (2 cases) of this group presented mostly with shortness of breath, cough (100%), tachypnea, which consides with lower respiratory tract infections. This goes with (Michael et al., 2012) [24] who found that fever is the most common manifestation of children with respiratory tract infections.

In our study, there is significant difference regarding dysuria, urgency, frequency and change color of urine between the studied groups being higher in group I in comparison to groups II because of presence of urinary tract infections in group I. This goes with (Ayazi et al., 2007) [25] who found that 90% of UTI cases suffered of dysuria, urgency, frequency.

Regarding the vital signs including temperature, respiratory rate and pulse in our study, there was high significant difference between the studied groups regarding temperature and respiratory rate being higher in group I in comparison to group II, .this goes with (Michael et al., 2012) [26] who found that there is significant difference between studied groups as regards temperature being higher in bacterial infections in comparison to control group.

Regarding the hematological data, our study revealed that WBCs was significantly higher in group (I) than control group (II) due to the presence of bacterial infections in group I.

Also regarding hematological data, our study revealed that the both groups suffered of anemia in different ranges, RBCs and Hg were less than normal because of renal affection in which anemia is a main feature of it this is in agreement with (Pankaj, 2003) [27] who found that most patients with chronic kidney disease are anemic.

On the other hand, there was no significant difference in platelet levels between the two groups.

In this study it is found that there is significant difference between group I (3 – 60) and group II (0-12) as regards CRP being higher in group I due to presence of infection than in group II without proven infection.

In our study, there is a significant difference between the studied groups regarding procalcitonin being higher in group I in comparison to group II.

In our study the increase of serum PCT occurred in both sexes and in all age groups and this in agreement with (Meisner et al., 2008) [28] who found that serum PCT supplies very rapid information in children with sepsis that is already available at admission in a critical care unit and this results were similar in both sex and age groups, from one month of age to adolescence.

In our study, we study procalcitonin levels as marker of bacterial infections in 30 patients (group I) with chronic kidney disease having infection (22 males and 8 females) and there was a significant difference between these patients and patients of group II (control group) who had no infections as regards procalcitonin level being higher in group I.

When statistically comparing the three parameters in our study (PCT, CRP and TLC) to determine the specificity, sensitivity and accuracy, the study shows that on constructing ROC curve for PCT at cutoff level of 0.63 ng/ml the sensitivity was 93.3%, specificity was 83.0%, PPV 82.4%, NPV 92.3 and accuracy was 86.7%. Also it shows that on constructing ROC curve for CRP at cutoff level of 12.0 the sensitivity was 93.3%, specificity was 60.0%, PPV was 70.0%, NPV was 90.0% and accuracy was 76.7%. The study also shows that on constructing ROC curve for TLC at cutoff level of 7.3, the sensitivity was 60.0%, specificity was 76.7%, PPV was 72.0%, NPV was 65.7% and accuracy was 68.3%.

Our work is in agreement with (Mori et al., 2012) [28] who found that at cutoff point of 0.5 ng/ml the sensitivity was 91%, specificity was 64%.

Procalcitonin performs better than leukocytic count and C-reactive protein for detecting serious bacterial infection among children with serious infection. Procalcitonin is better for ruling out serious bacterial infection than for ruling it in. Existing studies do not define how best to combine

procalcitonin with other clinical information. (Yo CH et al.,2012) [28].

5. Conclusion:

From the present study we can conclude that:

• In our study, serum PCT level was elevated in bacterial infections so, it can be an important marker to perform the diagnosis of bacterial infections.

• PCT is a reliable marker for early diagnosis and better management of bacterial infections across chronic kidney disease patients.

6. Recommendations

From the results of the present study, we recommend the following:

• Use of serum procalcitonin (PCT) as a biochemical marker to diagnose bacterial infections in patients with chronic kidney disease and start antibiotic therapy early to decrease morbidity and mortality of infections among these patients.

• Ruling out a bacterial infection remains troublesome and further studies with larger sample size and longer follow-up duration are needed to assess serum level of procalcitonin in early diagnosis, prognosis and follow up of bacterial infection among patients of chronic kidney disease.

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